VOLUME 101 • APRIL 1958 • NUMBER 4

A.M.A. ARCHIVES OF INTERNAL MEDICINE

Influenza
William J. Mogabgab

Inhibition of Cholesterol Biosynthesis in Man
George L. Curran and Daniel L. Azarnoff

Timely Versus Delayed Use of the Artificial Kidney
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Energy Costs of Activities in Health and Disease
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The Use of Diphenylhydantoin (Dilantin) Sodium in the Treatment of Ventricular Tachycardia
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Parietal Pleural Needle Biopsy
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Gastrointestinal Cancer
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Treatment of the Deep Mycoses
John J. Procknow and Clayton G. Loosli

Syphilis (To Be Concluded)
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A. M. A.
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Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

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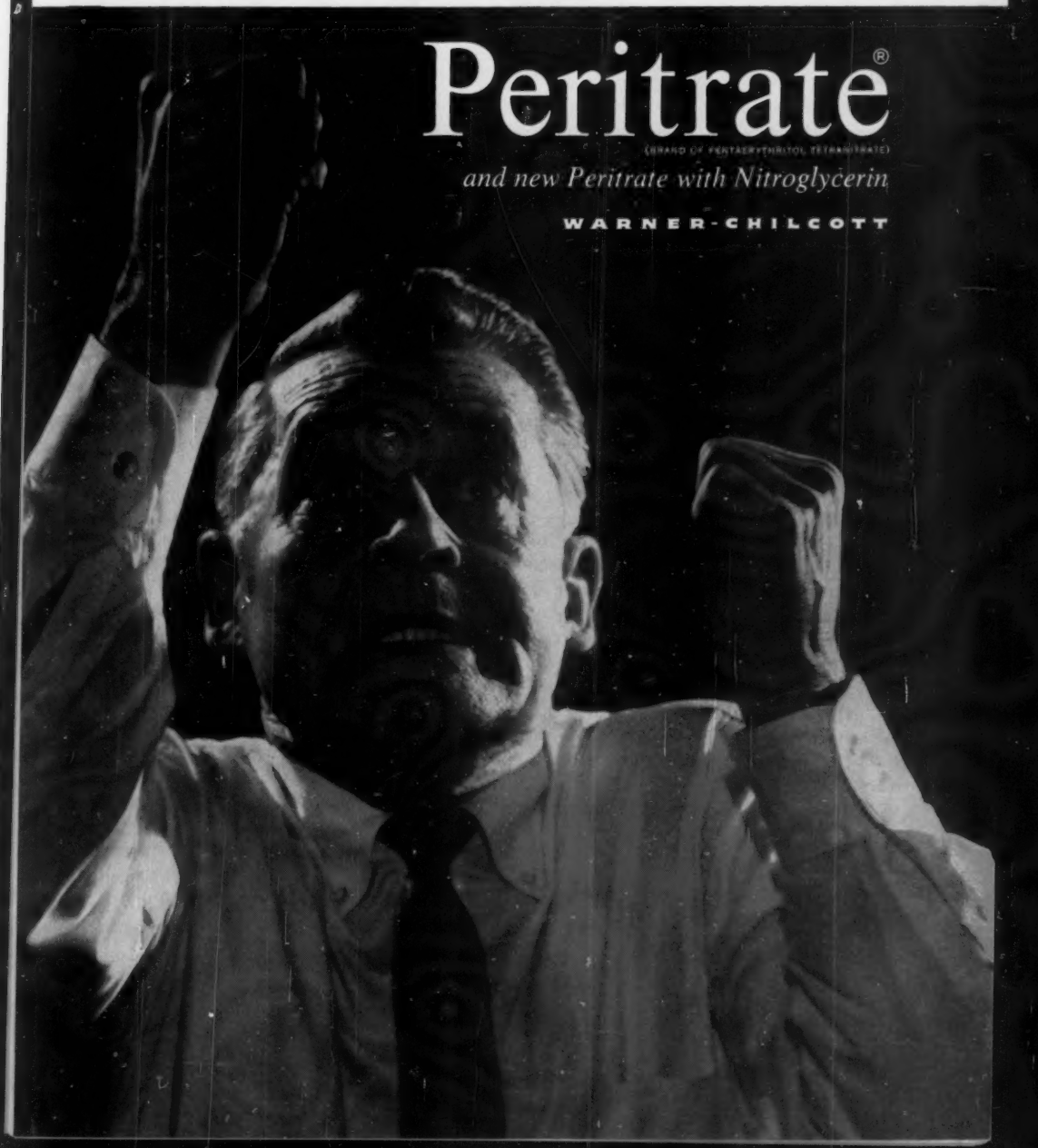

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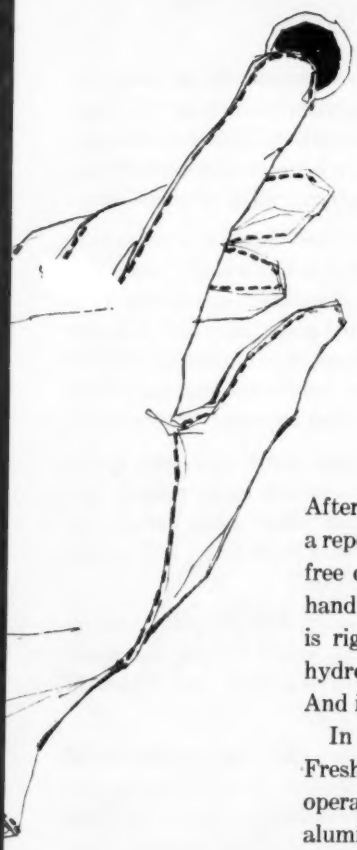

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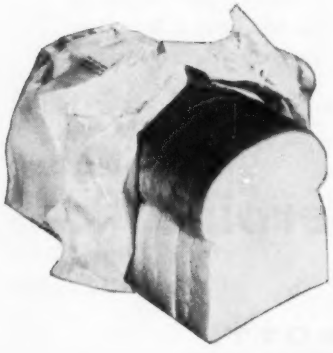

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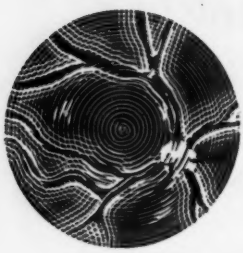

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* REFERENCE:
Crawley, C. J. *et al*: N. Y. State J. of Med. 55:23 (Dec.1) 1955: pp. 3461-3463.

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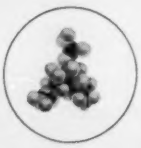

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A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Editorials

Influenza

Problems Still with Us

The appearance of another antigenic variant of Type A influenza (Asian or Far East) in a relatively nonimmune world population in the spring of 1957 was followed by the expected widespread dissemination of the virus. Despite immediate recognition of the initial outbreaks of illness with isolation and identification of the offending agent,[1,2] the tools were not at hand to prevent the disease from reaching pandemic proportions. Fortunately, the mildness and brevity of the disease and the infrequency of associated deaths remained fairly constant as the initial wave swept from country to country. Exceptions in isolated circumstances were probably due to factors other than change in the virus. Even though increasing virulence of the virus, severity of the disease, or frequency of complications were not the problems, an illness affecting millions of persons throughout the world deserves critical examination with all facilities available. The experience of the past year amply demonstrated the inability of vaccine to restrict the spread of a new antigenic variant of influenza even in those countries prepared for rapid vaccine production. Barring the development of universal influenza A and B antigens or of new methods for control or therapy of viral infections, it becomes obvious that more information is needed on the immediate as well as the long-term effects of influenza, the proper therapeutic measures, and the prevention of complications.

A better understanding of the mechanism of the clinical features certainly is required. Whether initial infection occurs in the nasopharyngeal mucosa in man is not known, although symptoms are sometimes referable to this area. Effects have been noted in the mucosal lining of the tracheobronchial tree from uncomplicated influenza, as well as associated deaths, and have consisted of areas of denudation and metaplasia with submucosal edema. The next step in disease mechanism is not clear. Clinical manifestations extend far beyond the respiratory tract, and frequently are minimal in that area. Does the virus spread to other organs, or is there a circulating toxin? The influenza virus particle itself has been shown to be toxic to laboratory animals, but a soluble toxin has not been associated with active infection.[3] Viremia has not been described in influenza in man, but this could be the result of insufficient effort in this direction or to its occurrence prior to onset of symptoms. Multiplication of this virus in other tissues seems less likely than poliomyelitis. The latter has been propagated in

Submitted for publication Dec. 12, 1957.
Department of Medicine, Tulane University School of Medicine.

most human tissues in culture, but growth of influenza virus has been demonstrated only in lung and kidney culture.[4,5] It would certainly be valuable to know whether viral multiplication takes place in the kidneys or other areas of the intact host. Although delirium is associated with severe cases and postinfectious encephalitis occurs, virus has not been recovered from the central nervous system of man. The potentiality exists, nevertheless, since certain strains can be adapted to growth in the mouse brain. Similar questions arise regarding susceptibility of pericardial epithelium or vascular endothelium.

Reasons for variation in severity of the disease in persons in the same epidemic are not known. Measurable differences in virulence of strains isolated in an epidemic have not been found. Possibly, there is less viral multiplication or neutralization of tissue-damaging activity in some persons, owing to antibody or nonspecific inhibitors or physical restriction of the disease to the initial site. The cause of the prolonged deep productive cough that sometimes continues after the acute phase of the illness has not been related to specific bacteria or preexisting pulmonary disease. Although this could be the result of the degree of mucosal destruction, secondary bacterial infection amenable to therapeutic measures is a good possibility. The cause of the severe and prolonged asthenia following the acute phase of the illness is still unknown. If this were shown to be produced by an altered tissue or metabolite, or deficit in a critical substance, the corrective measures might become obvious.

Perhaps more pressing is the acquisition of insight into complications, such as pneumonia, severe toxicity with hypotension, myocarditis, or precipitation of congestive heart failure. The fulminating nature of the bacterial pneumonia occasionally occurring in young adults or pregnant women and in persons in the extremes of life leaves little time for therapy, and delay can result in a fatal outcome. Certainly, promiscuous prophylactic antibiotic administration is not the answer to this infrequent, although serious, problem. Moreover, the peripheral leukocyte count is of doubtful aid, since it is sometimes elevated in uncomplicated influenza and frequently depressed in most of the pneumonia cases with fatal outcome. Precision in diagnosis of the causative agents involved in pneumonia deaths would be useful in outlining management. So-called sterile lungs from patients given antibiotics prior to death are of doubtful meaning in assessing the role of bacteria or the virus. The difficulty in cultivation of certain bacteria, such as Hemophilus influenzae; the significance of antibiotic-sensitive organisms cultured from the lungs of patients treated with the same antibiotics; the presence of bacteria in circumscribed areas and absence in others; the separation of contaminants from the pathogens, and the lack of quantitative measure of bacterial as well as viral infection are all problems in the way of elucidation of the etiology and mechanism of these pneumonias.

Therapy of severe toxicity with hypotension and cyanosis in patients with uncomplicated influenza or bacterial pneumonia provides an additional dilemma. The administration of adrenal corticoids might tide the patient through this phase; on the other hand, the incidence of bacterial pneumonia could be increased, or the degree of tissue damage, enhanced. Possibly, positive-pressure respiration would be of some value, but more pulmonary function studies are needed in patients with heart disease or pneumonia complicating influenza. How strictly should bed rest be enforced, and for how many days, in order to avoid sudden death, presumably due to postinfluenza myocarditis, is another important con-

sideration. What precautions should be taken by patients with heart disease, or pregnancy, or other conditions prior to an epidemic or during their illness must be determined. These are all real problems that must be answered. In each instance investigations of the disease mechanism are needed. Careful virologic and bacteriologic studies in conjunction with biopsy and autopsy material can be correlated with results of application of diagnostic and functional studies of all organs.

It is rather surprising that the influenza viruses, especially during the Asian strain pandemic, have not produced more virulent variants. Only a few intranasal passages in mice are required for adaptation, and pneumonia and death will then occur after infection. Evidently the factors are different in man-to-man transfer, for there are countless human passages of the virus during a world-wide epidemic.

There are still many problems associated with influenza vaccines. They have been prepared in the allantoic sac of the embryonated egg and, consequently, cannot be administered to persons sensitive to egg protein. This is only a minor phase of the difficulties, however. The incidence of local and systemic reactions of a severe, although not dangerous, nature is considerable and can usually be correlated with the amount of virus in the vaccine. More information is certainly needed on multiple small injections or the suitability of adjuvants, and the best route of administration and temporal spacing of inoculations must be determined. Other methods of preparation of the vaccine should also be investigated. The techniques and production methods for poliomyelitis vaccine in monkey kidney cultures should be helpful in the preparation of influenza vaccine from such a system. Efficacy or protection are difficult questions to answer. Low levels of antibody might produce herd immunity that will suggest a high degree of protective effect by a given vaccine. This could be insufficient safety for the special risk patient with other conditions. Much information has been obtained on production of titratable antibodies after vaccination, but this is not the real test of the material. Methods of inactivation and purification also vary and may affect the immunogenicity of the virus. What the role of circulating antibody might be in a disease affecting respiratory epithelium and, presumably, without a viremic phase is another matter for conjecture. Might the illness be restricted to an afebrile respiratory disease, would protection be complete, or would viral multiplication take place in the absence of any symptoms but still allow spread of the agent?

Subsidence of the Asian influenza epidemic should not cause these problems to be placed in the background. The facility of influenza viruses for antigenic variation will again set the stage for pandemic illness. Also, there are still many persons with little immunity against the Asian and the Denver strains of influenza A, and the degree of reciprocal immunity with these two viruses is probably low. Antibody levels to influenza B have now fallen to the point that outbreaks or epidemics can be expected. Even though the obvious influenza-associated deaths due to Asian virus were low in incidence, over-all mortality rates were clearly elevated by this illness. In nonepidemic years it is difficult to determine the effect of such respiratory virus infections on death rates. Undoubtedly, the life expectancy of patients with chronic disease is frequently shortened by these illnesses, and the results of many refinements in their management are accordingly nullified.

Extension of the above problems and results of the investigations of them can be made to other respiratory virus infections in many instances. Influenza can serve as a useful tool in this respect. Many of the features of adenovirus illness

are similar to influenza, and it is likely that complications could be handled in the same fashion. Undoubtedly, a multivalent respiratory disease vaccine would be a great asset not only in removing discomfort and economic loss but possibly in reducing degenerative disease. Whether complete recovery of bronchial mucosa occurs after infection, whether metaplasia remains and predisposes to anaplasia later in life, and whether permanent damage occurs in the cardiovascular or renal systems are all matters that should prevent us from being too philosophical about our attacks of "the flu."

WILLIAM J. MOGABGAB, M.D.
Division of Infectious Disease
1430 Tulane Ave.
New Orleans 12, La.

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Inhibition of Cholesterol Biosynthesis in Man

The treatment of atherosclerosis has for many years centered around attempts to lower the serum cholesterol level. The rationale for such therapy rests entirely on the statistically significant correlation which exists between coronary atherosclerosis and elevated serum cholesterol levels.[1] However, it has yet to be shown that reduction of serum cholesterol significantly modifies the course of coronary atherosclerosis. In fact, there is evidence that the serum cholesterol is not a true reflection of tissue cholesterol levels, and, therefore, definitive evaluation of any therapy can only be obtained from long-term clinical studies based on the incidence of myocardial infarction and on survival. Nevertheless, because of our almost total ignorance of the etiology of atherosclerosis, the best available field for the clinical investigation of atherosclerosis remains the experimental reduction of the total cholesterol stores of the body.

The cholesterol content of the body can be lowered in three ways:

1. Destruction of cholesterol within the body can be increased. To date no nontoxic means of increasing cholesterol degradation (e. g., by increasing the conversion to bile acids) has been found.

2. Reabsorption of biliary cholesterol from the intestine can be decreased. It has been demonstrated in animals that prolonged interference with cholesterol reabsorption by either sitosterols or nonsteroid means is counteracted by an increase in hepatic cholesterol synthesis with no net change in tissue levels.[2] It has also been shown that mixed soybean sterols [2] and β-sitosterol [3] are absorbed from the intestine and as such are potentially atherogenic, being found in the aorta of man after oral administration. The findings in experimental animals explain the failure of sitosterols to lower serum cholesterol levels in normocholesterolemic humans, as reported by Wilkinson.[4] The capacity of the liver to adjust within wide limits its production of cholesterol to the amount returned from the biliary-enteric circulation stresses the point that control of hepatic cholesterol synthesis is essential in any regimen for reducing the cholesterol content of the body.[5]

3. Endogenous cholesterol synthesis can be decreased. Since most of the cholesterol in the body is synthesized from fat, it seems obvious that if the fat in the diet is sharply reduced there should be a lowering of the cholesterol stores of the body. It is a well-recognized clinical fact that patients whose hypercholesterolemia without hyperlipemia is not due to liver, thyroid, or kidney disease will respond to a low-fat diet with some reduction in their serum cholesterol levels. More recently the clinical studies of Groen,[6] Kinsell,[7] Ahrens,[8] and Schroeder [9] have suggested that large amounts of unsaturated fatty acids also have a hypo-

Submitted for publication April 17, 1957.

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cholesterogenic action, at least insofar as serum cholesterol is concerned. The mechanism for this action of unsaturated fats is not clear, but it may be related to the fact that unsaturated fatty acids inhibit hepatic cholesterogenesis in vitro [10] more than saturated acids. This subject has recently been reviewed by Mann.[11]

Any form of treatment requiring either fat restriction or the addition of certain fats to the diet involves a major change in food habits on the part of the patient. The impracticality of successfully applying such dietary therapy to large numbers of persons seems apparent. Fortunately, it may be possible to reduce endogenous cholesterol synthesis by means other than by rigid dietary control synthesis in man.

With the original demonstration that cholesterol is formed from acetate molecules in the body,[12] it became apparent that the arterial atherosclerotic process might be modified by interference with cholesterol biosynthesis from fat. The validity of this working hypothesis was strengthened by the demonstration in rabbits that a reduction in excess aortic cholesterol could be accomplished by administration of an inhibitor of cholesterol synthesis.[13,14] The hypothesis may be stated as follows: Reduction of endogenous cholesterol synthesis by administration of a specific inhibitor of that process will produce a negative cholesterol balance and induce mobilization of cholesterol from arterial atheromatous plaques, thereby reducing those plaques in size and number. From data now accumulated it is possible to assess the requirements for an ideal inhibitor of cholesterol snythesis in man.

General Properties of the Inhibitor

The compound must, of course, be nontoxic at inhibitory levels. Water solubility and absorbability from the human gastrointestinal tract would be vastly advantageous, for the eventual definitive clinical study to evaluate the efficacy of the compound will probably involve investigations on large numbers of persons over a period of years. The drug must inhibit cholesterol biosynthesis in vitro within the limits defined in the next paragraph. In addition it must be shown to inhibit tissue cholesterol synthesis in man. It will not suffice to use serum cholesterol depression alone as an indication of the efficacy of the drug, inasmuch as too often the serum cholesterol is not a true reflection of the rate of tissue cholesterol synthesis or tissue (arterial) cholesterol content.[13,15] The problem in obtaining sufficient liver tissue from man in a normal nutritional state makes the demonstration of inhibition of human tissue cholesterol synthesis difficult. However, one method, utilizing human brain tumors, has been described recently,[16] and undoubtedly others will be devised.

Specific Properties of the Inhibitor

A compound inhibiting cholesterol synthesis can produce its effect either by competitive or by noncompetitive inhibition at any step in the intermediary metabolic synthesis of cholesterol:

$$\begin{array}{c} \text{Fat Catabolism} \\ \swarrow \quad \searrow \\ \text{Acetate} \longrightarrow \text{Acetyl-CoA} \longrightarrow \text{Acetoacetate-CoA} \longrightarrow \text{6-Carbon} \\ \text{Intermediate} \left(\begin{matrix} ? \\ ? \end{matrix} \begin{matrix} \beta\text{-Hydroxy-}\beta\text{-Methyl Glutarate} \\ \text{Mevalonic Acid} \end{matrix} \right) \xrightarrow{?} \text{5-Carbon Intermediate} \longrightarrow \\ \text{Squalene} \longrightarrow \text{Lanosterol} \longrightarrow \text{Zymosterol} \longrightarrow \text{Cholesterol} \end{array}$$

However, the sites of action of the ideal inhibitor are limited to those above acetoacetate and before the cyclization of squalene in the synthetic scheme. The

inhibitor must have its site of action above acetoacetate because in the intact animal and man most of the acetoacetate is derived from fat catabolism. Thus, blocking of the formation of acetyl-coenzyme A (CoA) from acetate or of acetoacetate from acetyl-CoA can never produce a major reduction in cholesterol synthesis in vivo. It is apparent that total inhibition of acetyl-CoA formation would be incompatible with life. At the other end of the intermediary scheme, inhibition after squalene has undergone cyclization to form the steroid nucleus would result in an accumulation of a steroid precursor of cholesterol. Atherosclerotic plaques contain a variety of steroids,[17] and it is known that sterols other than cholesterol are atherogenic.[2,18] It would seem possible that the ultimate result of inhibition after the cyclization of squalene would be to substitute some other sterol for cholesterol in the arterial plaque. In view of the limited capacity of the body to excrete squalene, it might be concluded reasonably that the ideal inhibitor of cholesterol synthesis must block one of the as yet ill-defined intermediary steps between acetoacetate and squalene.

With these criteria it is possible to evaluate those drugs which have been advanced as inhibitors of cholesterol synthesis. It should be remembered that at this time none has been proved to inhibit tissue cholesterol synthesis in man.

Recently, Δ^4-cholestenone [19] has been suggested as an inhibitor of cholesterol synthesis. This compound, however, produces inhibition of cholesterol synthesis by introduction of another sterol into the body and as such is subject to the previously outlined objections to inhibitors acting after cyclization of squalene.

The most widely used compounds have been similar to α-phenyl-N-butyric acid, introduced by Cottet.[20] Steinberg and Fredrickson [21] have shown that these compounds block the formation of acetyl-CoA from acetate. Although they inhibit radioacetate incorporation into cholesterol in vitro, such compounds cannot be expected to provide adequate inhibition of cholesterol synthesis in vivo, where most of the acetate for cholesterol synthesis is supplied as preformed acetyl-CoA from fatty acid catabolism. Careful clinical investigations by Fredrickson and Steinberg [22] and Grande, Anderson, and Keys [23] have shown these compounds to be ineffective in the reduction of human hypercholesterolemia.

Reports have shown α-p-biphenylylbutyric acid to be an effective hypocholesterogenic agent.[24] Tavormina and Gibbs [25] have presented data which show that the inhibition produced by this compound occurs after formation of a suggested 6-carbon intermediate (mevalonic acid). Confirmatory studies with other intermediates are needed to substantiate this enzymatic site of action. Otherwise, if α-p-biphenylylbutyric acid proves nontoxic in man, the criteria require only the demonstration of inhibition of human cholesterol tissue synthesis before clinical trial is warranted.

Diammonium oxytartratovanadate has been shown to inhibit the conversion of β-hydroxy-β-methyl glutarate to β-methyl crotonate, as well as the conversion of mevalonic acid to cholesterol.[26] This fact indicates that vanadium fulfills the criterion for the proper enzymatic site of action. The toxicity of vanadium at the dosage range necessary for cholesterol-synthesis inhibition in man remains to be determined. However, preliminary studies in this laboratory indicate that the effective dose of vanadium in man lies well below the range of toxicity. A vanadium concentration of only 0.0005 mg. per gram of dry liver tissue is necessary to obtain 70% inhibition of cholesterol biosynthesis. This minute effective

concentration illustrates the immense advantages in terms of therapeutics obtained from the use of a specific inhibitor of cholesterol synthesis.

To summarize, it is possible with presently available data to outline the requirements for a successful inhibitor of cholesterol synthesis in man. Further, there is encouraging evidence in animals which suggests that such inhibitors may prove practical therapeutic agents in the amelioration of atherosclerosis. Whether or not reduction of body cholesterol stores will lessen atherosclerosis remains an unproved hypothesis in man, but it seems clear that a rational approach to an answer lies in long-term clinical trials with effective specific inhibitors of cholesterol biosynthesis.

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Timely Versus Delayed Use of the Artificial Kidney

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The last several years have seen extensive study of the treatment of acute anuria, which has been summarized in thoughtful [1-3] and comprehensive [4] reviews. At the same time the technical aspects of hemodialysis have been refined and simplified to a point where the artificial kidney is applied in many centers routinely without significant morbidity or intolerance of the procedure.[5-9]

The initial scepticism concerning the beneficial aspects of this treatment [11-16] has been supplanted by a recognition of its life-saving potentialities by ever-widening circles of clinicians.[4,9,17-22] In view of the widespread interest in the artificial kidney it is surprising that agreement concerning the indications for it was in individual patients with acute anuria is lacking and that, indeed, indications for dialysis are entirely omitted in a recent review.[1] Are the signs and symptoms which form the clinical indication for use of the artificial kidney so elusive and ephemeral as to defy definition? While Kolff [23] in his earlier experience would restrict use of the artificial kidney to patients with acute anuria with serum K levels of 7.0 mEq. per liter or more, CO_2 content of 12 mEq. or less, and blood urea nitrogen (BUN) of 150 mg. per 100 cc. or more, he and others [6,18,23] now prefer to be guided by the clinical condition of the patient but have not presented detailed case histories or other evidence which would describe the clinical indications for dialysis. Yet others [4] have made "a rule of thumb to urge dialysis on the 5th or 6th day of virtual anuria." One wonders what the experiences might have been which caused the adoption of this rule. Until recently, Alwall [20] has performed dialysis only when anuric patients were in coma, but he proposes now to use it "more extensively." The Copenhagen school still considers a BUN of 200 as the primary criterion for dialysis.[17] During the Korean war the artificial kidney was used for the indication "uremia" (as distinct from hyperkalemia) as early as the third and fifth days of anuria.[21] In view of this widespread perplexity there would seem to be a real need for the critical evaluation of a well-documented series of cases of acute anuria from which it will be possible to draw conclusions concerning the indications for the use of the artificial kidney.

During the past four years about 130 patients with various types of severe uremia were treated by me with or without hemodialysis. Only 51 of these suffered from potentially reversible acute renal failure. Conclusions about the treatment of acute renal failure are therefore drawn from 34 patients with acute anuria who recovered with or without the use of dialysis and from 17 patients in whom potentially reversible acute tubular necrosis was found at autopsy. This paper will compare the treatment of patients who did and who did not recover from reversible renal failure and will attempt to identify errors in the management of the latter group and to formulate specific clinical situations which should call for hemodialysis without delay.

Clinical Material and Methods

The cases described here were seen during the last four years, when knowledge about good management of acute renal failure had become widely disseminated. The treatment of patients became my responsibility at varying phases after the onset of anuria-oliguria. In some instances I saw the patient only in a consulting capacity or my services were confined to dialysis treatment, which was

Submitted for publication July 22, 1957.

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carried out either at the Cedars of Lebanon Hospital or elsewhere. These patients will be identified in this paper with a (C) following the case number. The standard treatment of acute renal failure as practiced here is identical with standard practice in other centers.[1-8] It consists of limitation of fluids to the visible output plus 500 to 700 cc. for net loss (insensible perspiration minus water of oxidation). Patients are encouraged to take a nonprotein nonelectrolyte high-caloric diet; when this is impossible because of persistent vomiting, concentrated dextrose solution (up to 50%) is instilled into one of the large veins through indwelling plastic tubing. One unit of regular insulin per 5 gm. of dextrose is added. Potassium-absorbing resin was given by mouth or by retention enema in several cases. Water-soluble vitamins, including cyanocobalamin (vitamin B_{12}) and vitamin K, are administered parenterally. Serum electrolyte patterns are determined at frequent intervals. Symptomatic measures, such as high colonic irrigation, gastric suction, oxygen, and laxatives, are used whenever indicated. Drugs, including specific antibiotics, which may be needed for the control of urinary, local, or blood stream infections are administered with caution and awareness of their abnormal excretion. Testosterone is administered because of its potential protein-sparing effect. Transfusion of packed red cells or blood was not practiced in patients with a hemoglobin value above 8.0 gm/100 ml. The patients were weighed daily, if possible. All patients under my care were completely reevaluated twice daily. Electrocardiography and x-ray were used whenever necessary. The word "anuria" as used here describes a 24-hour urine production of less than 100 ml. "Oliguria" describes a daily urine volume below 500 ml.

Hemodialysis was performed with the portable Skeggs-Leonards artificial kidney[10,17] as modified here. Blood was simultaneously withdrawn and administered through a double-channel plastic catheter in the iliac vein, inserted via the saphenous vein. An average of 130 mg. of heparin was used in each dialysis. During the dialysis procedure the patients received a slow intravenous infusion of 5% dextrose, which afforded the opportunity for administration of drugs. Heparin was not usually neutralized with protamine sulfate unless this was indicated by a bleeding tendency. Dialysis fluid was used as formulated by Kolff.[28] Blood urea nitrogen, creatinine, uric acid, and serum potassium were often determined before and after dialysis; the concentration of these substances was also measured in samples of fresh and of used dialysis fluid. My fresh dialysis solution is now being analyzed for calcium before use because of the variability of the water content of the commercially available "anhydrous" $CaCl_2$.

Results

1. *Patients With Acute Anuria Who Recovered Without Use of Dialysis.*—Table 1 summarizes data of 19 patients with anuria who recovered without the use of dialysis. The duration of anuria-oliguria in these patients was from 3 to 11 days. One patient was in deep coma for 12 days and was treated with replacement transfusion on the third day of anuria in order to decrease the hypothetical nondiffusible toxins of toxemia of pregnancy. Diuresis followed administration of corticoids or corticotropin (ACTH) in five patients. The maximum serum creatinine was 18 mg/100 ml.; maximum BUN, 195, and maximum NPN, 230.

2. *Patients Who Recovered from Acute Anuria with Dialysis.*—In these 15 patients (Table 2) anuria-oliguria lasted from 9 to 39 days. Two patients were dialyzed twice. The highest NPN was 280 mg/100 ml. The highest BUN was 219 mg/100 ml. The highest serum K was 10.2 mEq. per liter. Three patients exhibited pronounced hypokalemia during the period of oliguria, which necessitated administration of potassium. Eight patients received corticosteroids or corticotropin during and after the period of anuria-oliguria, and there was onset of diuresis shortly after the beginning of steroid therapy in five. One patient (Case 27) had received 51,000 cc. of intravenous fluids during the first 25 days of anuria-oliguria, when his urine, gastric suction, and other visible fluid losses amounted to 8500 cc. Ultrafiltration removed 4500 cc. water from this patient. It is remarkable that this patient should have survived administration of about 24,000 cc. of excess fluid. One patient (Case 31), who survived 24 days of anuria-oliguria with the aid of two dialyses, is alive with severe brain damage which has been unchanged during the last two years and is localized mainly in the cerebellum.

In 12 of the 15 patients all physicians connected with the cases were of the opinion that hemodialysis was clearly life-saving and that the patients would not have recovered without this treatment.

TABLE 1.—*Patients Who Recovered from Acute Anuria Without the Use of Dialysis*

Case	Sex	Age	Probable Cause of Anuria	Duration of Anuria-Oliguria, Days	Highest BUN, NPN, Creat., Serum K	Treatment Other than Standard; Remarks
1 (C)	M	63	Dehydration, electrolyte imbalance	5	NPN 205 Creat. 7.5	7,000 ml. fluid deficit replaced
2 (C)	M	62	Surgery f. aneurysm abd. aorta	7	NPN 165 Serum K 9.2 CO_2 12.5 mEq./L.	
3	F	33	Resp. infec. antibiotic therapy	4	BUN 95	
4 (C)	F	78	Dehydration	3	BUN 85 Serum K 7.8	Pt. died from cerebral hemorrhage 3 days after onset of diuresis
5	M	42	Hematomata	6	BUN 110	Massive pulmonary edema treated successfully with digitalization
6 (C)	F	48	Transfusion	11	BUN 195 Electrolytes normal	
7 (C)	F	44	Hypovolemia postop.	3	BUN 90	2,500 ml. plasma I. V.
8 (C)	M	79	Dehydration	4	BUN 110 Creat. 6.2	I. V. serum albumin and fluids
9	F	33	CCl_4 exposure	8	NPN 230	Multiple ecchymoses & gastrointestinal hemorrhages at height of uremia; electrolytes normal
10	F	31	Toxemia of pregnancy	5	NPN 130 Creat. 9.1	Electrolytes normal; Pt. comatose 12 days; clearing of coma 1 day after corticoid therapy started
11	M	39	Acute nephritis	7	BUN 120	Electrolytes normal; reversal of pulmonary edema & start of diuresis after corticoids
12	F	57	Pulmonary infection	4	BUN 118	Electrolytes normal
13 (C)	F	45	Transfusion	8	BUN 145	Electrolytes normal
14 (C)	F	53	Shock, transfusion	5	BUN 90 Na 122 mEq./L.	"Shock" manifested by normotensive episode in hypertensive, after injuries
15	M	64	Shock, transfusion	4	BUN 116	Corticoid therapy 3 wk.; 50% I. V. dextrose for 12 days (unable to swallow)
16	M	49	Exacerbation of chr. nephr.	3	BUN 125 Creat. 18	Pt. in pul. edema and coma; clearing of pul. edema & onset of diuresis after cortic. and 50% dextrose I. V.
17	F	28	Transfusion	8	Creat. 10.5	Na 120 mEq./L.; CO_2 14; 50% dextrose I. V. for several days; corticotropin started on 6th day of anuria
18	M	64	Obstruction of outflow after prostatectomy	8	BUN 105	Electrolytes normal
19	F	74	Shock, bile peritonitis, empyema of gallbladder, cholecystotomy	6	NPN 150 K 7.2	Pt. overhydrated for 5 days postop.; coma, pul. edema; infusion of 50% dextrose, calcium, hydrocortisone, full recovery

The indications for dialysis are summarized in the Table. It is readily apparent that we attempted to defer dialysis until the patients' condition compelled us to use it. Severe hyperkalemia was the primary indication in three cases (Cases 20, 28, 34); severe neurological signs with varying degrees of circulatory embarrassment and azotemia caused us to use dialysis in six patients (Cases 21, 22, 23, 31, 33, 34). (It is not really possible to separate neurological signs from other abnormalities as primary indications for dialysis.) In six patients (Cases 23, 25, 26, 27, 28, 29) cardiovascular abnormality was the primary reason for dialysis; one patient was dialyzed because of his complex picture of restlessness, vomiting, and mounting azotemia, which is known to precede the convulsions, coma, and other features of uremia.

Patients 23 and 34 suffered from fairly voluminous intestinal hemorrhage (Case 23, about 2000 cc. tarry stools; Case 34 lost 1000 cc. frank blood via gastric suction) before and during the procedure; the hemorrhages were not aggravated by hepa-

TABLE 2.—*Patients Who Recovered from Acute Anuria; Treatment Included Dialysis*

Case	Sex	Age	Probable Cause of Anuria (or Acute Uremia	Duration of Anuria-Oliguria, Days	Highest NPN,BUN, Creat., Serum K	Dialysis Performed Day After Onset of Anuria-Oliguria	Results of Dialysis; Remarks
20	M	58	Bilateral ureteral obstruction (carcinoma)	9	K 10.2 BUN 115	8th day; indication: hyperkalemia	Serum K 6.3 after dialysis; ureteral catheters passed on 9th day of anuria; massive diuresis; corticoid therapy
21	F	66	Ruptured common duct; bile peritonitis, shock	14	BUN 180	5th day; indication: coma, gallop rhythm, high BUN	Dialysis: BUN from 180 to 60 mg./100 ml.; Pt. comatose before dialysis; Na 112; serum K low (2.7 mEq./L.) dur-anuria, necessitating I. V. potassium therapy; I. V. 50% dextrose 14 days; corticoid therapy
22	M	16	Acute nephritis; bacteremia after dental extract	16	BUN 212 CO_2 12	12th day; 16th day 1st coma, cardiac failure; 2d cont'd coma; mounting azotemia	BUN lowered 212 to 105 and 186 to 79 by dialyses; pt. arrived in coma, pul. edema, gallop, pulse 150; serum K 2.3 mEq./L. on 12th day; I. V. potassium therapy; I. V. 50% dextrose drip for 10 days; diuresis started & coma re-versed 1 day after start of corticoid therapy
23	F	44	Acute nephritis, cause unknown	13	BUN 190	8th day; indication: papilledema, pul. edema, incr. venous pressure, incr. reflexes	BUN lowered from 190 to 54 by dialy-sis; no electrolyte abnormalities; mul-tiple ecchymoses and gastrointestinal bleeding before & during dialysis, stopped after
24	F	56	Unknown, massive hematoma of abd. wall & into gastrointestinal tract	18	Creat. 17.8	16th day; indications: coma, convulsions, azotemia	Dialysis: creat. before 17.8, after 7.8; serum K 2.1 mEq./L. during anuria, treated with I. V. potassium; corticoid therapy after 12 days of anuria
25	F	48	Resp. infection; antibiotic therapy; acute nephritis	None	NPN 180 Creat. 15	Indications: pul. edema, convulsions, stupor	Pt. dialyzed in severe peripheral and pulmonary edema; striking clinical improvement & full recovery; electro-lytes normal; NPN 190 to 80
26 (C)	M	16	Purpura of kidney & other systems	19	Creat. 12	9th day; indications: pul. edema, azote-mia, moderate	Good clinical response; relatively poor efficiency of dialysis
27 (C)	M	58	Acute nephritis after resp. infection, anti-biotic therapy	Anuria 16; anuria + oliguria 39	NPN 280 Creat. 22	23d day; indications: pul. edema, azote-mia arrhythmia	NPN 280 to 110, creat. 22 to 10; dial-yzed with marked pul. edema & cya-nosis, heart block; corticoid therapy; pt. massively overhydrated during anuric phase; dialysis removed 4,500 cc.
28	M	51	Edematous obstruc-tion of ureters, pyelonephritis	10	BUN 115 K 9.2	8th day; indications: hyperkalemia, confusion	BUN 115 to 60, K 9.2 to 5.2; diuresis & clearing of uremia after nephros-tomy 2 days post dialysis; pt. died 4 wk. later from generalized sepsis; no corticoid therapy
29	M	50	CCl_4 exposure	12	BUN 212 Creat. 16	10th day; indications: pul. edema, azotemia	BUN 212 to 102, creat. 16 to 9.2; severe pul. edema cleared by dialysis; no corticoid therapy
30	M	67	Transfusion	10	BUN 219	8th day; indications: twitching, pul. edema, cardiac failure	BUN 219 to 99; creat. 13.5 to 8; K 6.9 to 4.3; twitching, gallop & pul. edema before dialysis, reversed by it
31 (C)	F	62	Transfusion	23	BUN 160	11th day; 18th day; indications: convul-sions, coma	BUN 160 to 35; BUN 150 to 32; elec-trolytes normal throughout; pt. coma-tose & convulsing before each dialysis; diuresis after steroid therapy on 23d day; severe residual CNS damage
32	M	35	Chlorpromazine or tetraethylthiuram disulfide	12	BUN 185 Creat. 21 K 7.3	14th day; indications: restlessness, vomit-ing; mounting azotemia	BUN 185 to 85; corticoid therapy from 6th to 21st day; urine output when dialyzed 1,300 cc. but pt. restless, vomiting, friction rub, confused
33 (C)	M	60	Reflex (?) anuria associated with solitary kidney, pelvic stone, & lithectomy	9	BUN 92 Creat. 11.7 CO_2 13.0	Dialysis performed 7th day; indications: acidosis, semicoma, incr. reflexes	BUN to 52; CO_2 to 23; pt. semicoma-tose before dialysis, awake and ration-al thereafter; full recovery; pt. has essential hypertension (normally 200/100)
34	F	39	Transfusion reaction (0 hr. isoagglutinins)	11	BUN 210 K 8.7	Dialysis performed 8th day; indications: restlessness, confusion, blood chemistry, supraventricular tachycardia	BUN to 70; K to 5.8; full recovery

TABLE 3.—*Patients with Potentially Reversible Renal Lesions Who Died as a Result of Renal Failure*

Case	Sex	Age	Cause of & Onset of Anuria-Oliguria (Days Before Death)	Mechanism of Death	Maximum BUN, NPN, K, Lowest CO_2	Dialysis	Controversial Feature of Treatment
35 (C)	F	48	Transfusion (13)	Pul. edema	BUN 140 K 6.8 CO_2 16.0	Yes; 13th day	Dialyzed when in pulmonary edema; dialysis too late & ineffective; pt. was also moderately overhydrated; lethal pul. edema occured 12 hr. after first signs of circulatory embarrassment were temporarily improved with digitalization
36 (C)	M	41	Transfusion (6)	Convulsions	NPN 110 K 6.8 CO_2 22	No; thought K could be held down and pt. would recover with conservative therapy	Infusion of 50% dextrose plus insulin & calcium gluconate improved twitching & dyspnea on 5th day; ECG showed no evidence of K toxicity on 6th day; twitching & convulsions suddenly occured on 6th anuric day; pt. probably died during hypotensive episode secondary to convulsion; pt. should have been dialyzed
37	M	34	Carbon tetrachloride (7)	Ventricular fibrillation	BUN 94 Creat. 16.9 Serum K 7.4, rose to 8.8 within 12 hr.	No	Dialysis deferred because of rising urine output (250 cc. in 8 hr.) & because it was thought K would be controlled with dextrose-calcium-insulin I. V.; died suddenly during preparation for dialysis, which was decided on when 2d serum K became known; procainamide (Pronestyl) ineffective
38	M	52	Antibiotics ? (19)	Coma	NPN 320 Creat. 22	No; diuresis on 8th day but without clinical improvement	Pt. comatose 19 days; died when creatinine and NPN almost normal; electrolytes normal throughout; should have been dialyzed earlier to preclude or reverse coma
39 (C)	M	23	Prolonged shock, multiple intestinal perforations, & left nephrectomy; shotgun accident	Circulatory K toxicity 4 days	K 8.2 Na 136 CO_2 18 BUN 95	No	ECG with marked evidences of K toxicity; QRS 0.18, absent P waves; dextrose-insulin-calcium infusion started; pt. died few minutes after start of infusion before dialysis could be started
40 (C)	F	45	Transfusion 14th day	Pul. edema 14 days	BUN 95 Electrol. normal	Yes; 13th day; BUN to 55; pt. in pul. edema before & after dialysis	Diuresis 8 days after onset of anuria; coma and pul. edema developed while pt. was diuresing (max. daily output 1,800 cc.) & while she was given good conservative management; should have been dialyzed when confusion & pul. edema were first noted while azotemia increased in spite of diuresis
41	M	63	Transurethral prostatectomy; transfusion; hemolytis	Central nervous. 12 days	NPN 245 K 7.0	9th day; NPN to 112; electrol. normal until death	Twitching started 5th day & continued until death, becoming steadily worse; electrolytes normal 12th day; NPN 142 12th day; autopsy showed cerebral edema & mild chronic pyelonephritis as well as tub. necrosis; should have been dialyzed when twitching first noted (delay because of bleeding from prostatic bed)
42	M	42	Transfusion; undiagnosed rheumatic carditis	Circulatory and central nervous. 7 days	NPN 195 K 8.5	5th day; K 8.5 to 6.6; NPN 195 to 123 (235 mEq. K removed, 90 gm. NPN removed by dialysis)	Pt. dialyzed in coma & tachycardia 130; prompt improvement and 550 cc. urine next day; recurrence of coma 7th anuric day; K up to 8.4; ventric. fib. while preparing for second dialysis
43 (C)	M	55	Transurethral prostatectomy; hemolysis	Pul. edema. 8 days	NPN 135 K 6.8 CO_2 18	No	Pt. passed 180 cc. urine on last day of life; died few minutes before I arrived at bedside; received 1,200 cc. fluid daily for 8 days; should have received less fluid & been dialyzed at the first sign of resp. embarrassment
44 (C)	M	27	Shock, transfusions after auto accident (5)	Pul. edema	NPN 98 Electrol. normal	No; pt. died as artificial kidney therapy was starting	Pt. received 7,500 cc. fluid I. V. in 4 days when he put out only 200 cc./day; earlier dialysis might have corrected this error in treatment; ultrafiltration should have been used
45 (C)	F	20	Shock, transfusion after induced abortion (5)	Pul. edema	NPN 130 K 7.2	No; pt. died as artificial kidney was starting	Pt. received 6,500 cc. fluid in 5 days of anuria; unconscious & cyanotic when seen; earlier dialysis & ultrafiltration might have corrected azotemia & error in management (overhydration); total pulmonary edema on autopsy

TABLE 3.—*Patients with Potentially Reversible Renal Lesions Who Died as a Result of Renal Failure*—Continued

Case	Sex	Age	Cause of & Onset of Anuria-Oliguria (Days Before Death)	Mechanism of Death	Maximum BUN, NPN, K, Lowest CO_2	Dialysis	Controversial Feature of Treatment
46	F	28	Cesarean section; transfusion (7)	Pul. edema; sudden card. arrest	NPN 230 BUN 145 K 7.6	No	Erroneous diagnosis of pulmonary embolism because of loud 2d pulmonic sound, heaving precordium, & high venous pressure; erroneous diagnosis of pelvic phlebitis because of regional swelling & tenderness; dialysis deferred because it was thought serum K would be controlled with dextrose-insulin-calcium I. V. & because she improved with digitalis-oxygen
47 (C)	F	34	Induced abortion; transfusion (21)	Circ. & CNS damage	NPN 185 BUN 145	Yes; 21st day; no clin. improvement	Electrolytes normal throughout; confusion on 15th day; diuresis (1,200 cc./day) on 16th day; clinical condition not improved with diuresis; 3,000 cc. urine on 20th day; completely disoriented & confused, tachycardia 140, not improved by dialysis; died 8 hr. after dialysis; should have been dialyzed when confusion & tachycardia started
48 (C)	F	45	Induced abortion; peritonitis (14)	CNS damage; pul. edema	BUN 272 CO_2 13	Yes; 8th day; BUN 229 to 45; marked clinical improvement	I strongly urged second dialysis on 13th day but attending physician did not approve; he expected spontaneous cure with continued conservative therapy because of "incipient diuresis" (250 cc./24 hr.); pt. should have had repeat dialysis
49 (C)	M	32	Prolonged shock; multiple fractures & hematomata (14)	Coma & pul. edema	NPN 265	Yes; 7th day; poorly tolerated hypotensive reactions because of faulty dialysis fluid (low Ca)	NPN lowered from 265 to 180 by dialysis, with clinical improvement; pt. died while 2d dialysis was being arranged; NPN 365, K 8.2 on day of death; urine 900 cc. day of death; patient should have had 2d dialysis in time
50 (C)	M	52	CCl_4 (11)	Convulsions; coma, pul. edema	Creat 12 K 7.4 Na 112	No; peritoneal lavage 10th day without effect	I strongly urged hemodialysis on 9th day but was overruled by 6 colleagues who expected spontaneous recovery with conservative management
51 (C)	M	71	Resection of aneurysm of abdominal aorta; 18 transfusions; Trf. reaction? (10)	Coma, acidosis	NPN 160	No; pt. died 5 min. before start of hemodialysis	Should have been dialyzed sooner; pt. had good conservative therapy (40% dextrose I. V. + insulin) and was not overhydrated

rinization and dialysis and were arrested within four hours after the heparin had been neutralized with protamine sulfate.

3. *Patients with Acute Reversible Renal Disease Who Might Have Survived with More Appropriate Therapy.*—When patients survive after an episode of acute renal failure it is not easy to take issue with the therapeutic management employed. On the other hand, the question must be posed as to what went wrong when patients do not survive such episodes, when the autopsy findings show that the patients were suffering from potentially reversible lesions of the kidney and when death as a result of associated primary pathology is not likely.

Representative histories of 17 cases (Table 3) seen here will be narrated individually in addition to the summary in the Table.

CASE 38.—A 52-year-old man underwent retrograde pyelography because of ureteral gravel. He was otherwise in good health except for mild hypertension of long standing (170/100). Two days after the procedure he developed a slight fever and dysuria. He received two oral doses of 500 mg. of oxytetracycline. Within three hours after the first dose he developed a fever, with temperature of 106 F, which was accompanied by intense backache and malaise. Anuria was noted the next day. The patient received adequate management and was seen in consultation four days after the onset of anuria, when he appeared conscious and not edematous; there was no evidence of cardiovascular embarrassment, neurological abnormality, or electrolyte imbalance, and the NPN was 170. On the seventh day of anuria the patient was transferred to my care when he was comatose, covered with a papular rash, his serum creatinine was 22 mg/100 ml., and the NPN, 320. The electrolyte pattern was normal. Because of the apparently allergic eruption the patient was treated with 150 mg. of cortisone intramuscularly while dialysis was arranged. Shortly after receiving the injection of cortisone, the patient awoke from his deep coma and conversed rationally but relapsed

into coma after a lucid interval of about six hours. At the same time diuresis commenced (eighth day) and the eruption subsided. Dialysis was then postponed because of the sudden improvement of the patient's condition. In spite of the increasing diuresis the patient continued in coma but maintained normal electrolyte patterns, blood glucose levels, plasma proteins, and blood pressure. During the following days massive diuresis developed and the serum creatinine decreased from the original level of 22 mg/100 ml. to a final value of 2.8 mg.. Electrolyte and water replacement was regulated with great care. In spite of this treatment the patient did not awaken from the comatose state and developed aspiration pneumonia. Tracheotomy was performed in order to aid with the tracheal toilet; specific antibiotics were administered; spinal puncture was performed for diagnostic reasons. On the 16th day after the onset of anuria jaundice was noted. In spite of all care and in the face of normal serum electrolytes, blood glucose, and plasma proteins, the coma persisted, and the patient died 19 days after the onset of anuria, when the uremia had almost completely receded. Autopsy showed only slight cerebral edema and the typical lesions of acute tubular necrosis in kidneys which also showed some nephrosclerosis. There was extensive fatty infiltration of the liver and some central necrosis of the liver lobules.

Comment.—This patient died of uremia caused by acute tubular necrosis which must be attributed to the treatment with oxytetracycline. Acute uremia caused brain damage, which did not heal while the uremic state was subsiding. Clinical evidence of hepatic injury became apparent only when the patient had been comatose for 10 days. It is felt that his life would have been saved if dialysis had been performed before the cerebral injury had become irreversible. An interesting accessory finding in this case is the temporary reversal of coma after the administration of cortisone.

Case 41.—A 63-year-old man had been in good health except for prostatic hypertrophy with signs of obstruction. He underwent a transurethral resection (distilled water used for bladder irrigation) during which profuse bleeding from the prostatic bed was encountered, which necessitated several transfusions. On the first postoperative day oliguria was discovered and free hemoglobin was found in his serum. I saw this man on the fifth postoperative day, when his NPN was 145 mg/100 ml.; serum Na, 140 mEq. per liter; K, 5.8 mEq.; Cl, 95 mEq.; Ca, 3.0 mEq., and the CO_2 14 mEq. He was conscious and rational but exhibited marked reflex hyperactivity and occasional twitching. Dialysis was postponed because of bleeding (200 cc. per day) from the prostatic bed. On the ninth postoperative day dialysis was started because his twitching had become more intense; the serum potassium had mounted to 7.0 mEq. per liter, and the NPN had risen to 245 mg/100 ml. At this time his urine output was 200 cc. per day. Dialysis was successful from the chemical point of view (NPN lowered from 240 to 115 mg/100 ml.) but completely useless clinically. The twitching became more intense and was localized primarily in the right upper extremity. On the 12th postoperative day the urine output was 300 cc.; the NPN had risen to 142 mg/100 ml.; the serum Na was 142 mEq. per liter; the serum K, 5.2 mEq.; the CO_2 content, 27 mEq.; the Cl, 95 mEq.; the Ca, 4.5 mEq., and the phosphates, 8 mg/100 ml. The patient died during a convulsion four hours after the above blood specimen was procured. Autopsy showed cerebral edema, silent duodenal ulcer, and renal lesions consistent with healing tubular necrosis superimposed upon chronic interstitial (pyelo-) nephritis.

Comment.—Neurological signs of uremia began in this patient after only four days of anuria, were probably caused by increasing cerebral edema, were not related to pathological levels of serum electrolytes, and had become irreversible by dialysis only nine days after the onset of anuria. The patient died only four hours after blood samples had revealed relatively normal electrolyte pattern and relatively low NPN. It is believed that earlier dialysis would have reversed the cerebral edema or precluded its aggravation, thereby extending his life span sufficiently to afford his injured kidneys time to heal. Persistent bleeding from the prostatic bed influenced against earlier dialysis. In retrospect the danger of delaying dialysis would outweigh the potential danger of hemorrhage.

Case 42.—A 31-year-old rancher was suffering from recurrent backaches which were believed to be caused by a herniated disk. During an operation on his lumbar spine he received 2 units of incompatible blood, and he became anuric two days later. When seen by me seven days after the operation, he was comatose and in mild pulmonary edema, with a heart rate of 130; serum K, of 8.5 mEq. per liter, and NPN, 195 mg/100 ml. During the preceding six days he had received an average of 500 cc. of water, 200 gm. of dextrose, and 80

units of corticotropin per day. Because of the critical condition dialysis was started immediately. The patient developed recurrent hypotensive episodes while the artificial kidney was being used which necessitated the administration of pressor agents. The blood pressure stabilized after administration of corticotropin and of cortisone, and the patient appeared improved after dialysis. The NPN had fallen from 195 to 123 during the dialysis and the K had fallen from 8.4 mEq. per liter to 6.5 mEq.; these relatively modest chemical changes occurred in the face of a recovery of 235 mEq. of K and 96 gm. of nitrogen in the dialyzing solution. On the day after dialysis the patient appeared improved, produced 550 cc. of urine, and conversed rationally. Two days after dialysis (ninth postoperative day, seventh day of oliguria), the serum K had risen to 7.9 mEq. per liter; the creatinine was 15.7 mEq. the serum Na, 133 mEq., and the CO_2 16.8 mEq. The patient had returned to the comatose state. While repetition of the dialysis was under consideration and while a sudden recurrence of the hypotension was being treated with pressor agents, the patient developed a bundle-branch block and died shortly afterward. Autopsy showed the typical renal lesions of hemoglobinuric tubular necrosis and also active rheumatic carditis with involvement of the myocardium and of the aortic valve.

Comment.—Acute tubular necrosis caused by a transfusion accident was complicated in this case by coexistence of unrecognized active rheumatic carditis and valvulitis. Therapy with corticotropin was started shortly after the transfusion accident. It seems clear that because of this rheumatic state this patient should have received larger doses of corticosteroids here than he actually did receive; his cardiovascular status improved transiently following corticotropin and corticoid administration, but because of then-prevailing conceptions about the possible disadvantages of corticoid therapy the dosage of steroids was reduced after dialysis. Hemodialysis did not decrease the serum K or the serum NPN commensurate with the large amounts of K and N removed in the dialysis fluid; in view of this fact it appears questionable whether or not repetition of the dialysis would have prolonged his life. The reversibility of the renal lesion is attested by the 550 cc. of urine on the day after dialysis. More energetic and more timely treatment might have been life-saving.

CASE 46.—A 28-year-old woman underwent cesarean section and received 1 unit of blood. Chills and fever occurred, but she did not become oliguric. She was seen seven days after the operation, when she had passed 1000 cc. of urine during the preceding 24 hours; was in slight pulmonary edema, and appeared stuporous, cyanotic, and intensely dyspneic. Her reflexes were not markedly hyperactive. There was no peripheral edema. The perineal and inguinal regions were exquisitely sensitive and tender. There was marked distention of the peripheral veins, enlargement of the liver, very loud pulmonic second sound and a palpable pulmonary tap in the second left intercostal space. NPN was 230 mg/ml.; BUN, 145 mg.; Na, 132 mEq. per liter; K, 7.6 mEq.; CO_2, 11 mEq.; Ca 4.2 mEq., and a chest plate showed pulmonary edema and bulging pulmonary artery segment. A consulting cardiologist and I proposed the diagnosis of acute tubular necrosis of the kidney secondary to transfusion reaction and of multiple pulmonary embolism secondary to pelvic thrombophlebitis. Dialysis was deferred because it was felt that her life was menaced not so much by the existing uremia as by right heart strain due to multiple pulmonary embolization and elevated pulmonary resistance. She received digitalis and oxygen, with prompt improvement of cyanosis and pulmonary edema, and was otherwise treated in the standard manner, which included 50% intravenous dextrose drip with insulin and calcium. One day after admission she was talking with me, when there was sudden syncope and death. At autopsy the lungs exhibited moderate pulmonary edema, but no emboli were found. The heart was normal; there was no thrombophlebitis or other obvious sources of embolization. The kidneys showed the typical lesions of acute tubular necrosis secondary to hemolysis.

Comment.—Earlier dialysis might have been life-saving in this patient. Dialysis was not performed in this anuric patient because pulmonary hypertension and right-heart-strain pattern were so severe as to suggest pulmonary embolization. At autopsy no pulmonary abnormality was found, to our surprise. Pulmonary vasoconstriction simulating embolization was part of the picture of acute uremia.

It has been recognized for some time that uremic toxicity can cause cardiovascular dysfunction, including tachycardia, heaving precordium, increase in pulse pressure, and accentuation of heart sounds, particularly of the second pulmonic sound.[25] It can be learned from this patient that the signs of

right ventricular strain can occur in uremia to an extent which imposes the differential diagnosis of pulmonary embolization. The mechanism of the apparent right ventricular strain is not known and deserves further investigation.

CASE 47(C).—A 34-year-old woman received an incompatible transfusion because of prolonged blood loss after an induced abortion. She became anuric one day after the transfusion and was seen by me on the 15th day of anuria, when her NPN was 150, the serum electrolytes essentially normal, and she appeared mildly confused. I would at present have dialyzed immediately, but at the time continued conservative regimen was advised and dialysis was recommended if the patient would show no improvement of her mental status within two days. This advice was disregarded by the attending physicians, who looked forward to a spontaneous clinical improvement, inasmuch as diuresis had set in on the 16th day after admission (1200 cc. per day). There was, however, no commensurate clinical improvement. Twenty-one days after the onset of anuria she was transferred to my care. She had put out 3000 cc. urine during the preceding 24 hours. At this time her pulse was 150, and she was disoriented and noisy, with very hyperactive reflexes. NPN was 185; BUN, 145, and serum electrolyte pattern essentially normal. Immediate dialysis was performed. During and after the dialysis, which reduced the BUN to 80 mg/100 ml., the heart rate never fell below 150, while the temperature was normal. ECG disclosed sinus tachycardia. Blood cultures taken before and after the dialysis were sterile. The patient's mental condition did not improve during or after dialysis. The blood pressure was well maintained until eight hours after the termination of dialysis, when the patient suddenly developed hypotension and died before pressor agents could be administered. Autopsy showed the typical lesions of acute tubular necrosis but no other abnormalities of the nervous or circulatory systems which would have served to explain the clinical course.

Comment.—This case emphasizes the fact that fatal injury of the circulatory and central nervous systems can occur in the presence of relatively low azotemia even with essentially normal serum electrolytes and can deteriorate in spite of copious and increasing diuresis. It seems clear that earlier dialysis could have prevented the establishment of irreversible lesions which must have caused death.

CASE 48(C).—A 45-year-old housewife underwent an induced abortion, with resulting peritonitis. This was treated with antibiotics. She became anuric and was seen by me after eight days of anuria, when she was confused, was in mild pulmonary edema, and exhibited a BUN of 229 mg/100 ml. but no marked abnormality of her serum electrolyte pattern except CO_2 16 mEq. per liter. Immediate dialysis was performed, with resulting marked improvement of the chemistry (BUN, 45) the pulmonary edema, and the mental condition. Five days after this dialysis (13th day of oliguria), when the BUN had again risen to 272 mg/100 ml., she was stuporous and confused and had periods of Cheyne-Stokes respiration; the CO_2 was 13 mEq. per liter and the serum K and Na, normal. Another dialysis was strongly recommended by me but declined by the attending physician because of "incipient" diuresis (250 cc. of urine in 24 hours) and because of the still normal electrolyte pattern. The patient died suddenly 14 days after the onset of anuria. Autopsy showed acute tubular necrosis of the kidney as well as healed peritonitis and the expected changes of the uterus.

Comment.—Repetition of dialysis would probably have extended the life span and would have permitted recovery of renal function. It is evident that the first dialysis improved the clinical condition remarkably. A second dialysis was postponed because of the same spurious reasoning which causes delay in so many other dialyses. Incipient diuresis is not a reliable criterion which would argue for delay of any dialysis when other indications make it necessary.

CASE 51.—A 71-year-old man underwent a resection of the abdominal aorta and of both iliac arteries because of severe aneurysmal dilatation, which also involved the ostium of the left renal artery. Eighteen units of blood was administered during the operation; the systolic pressure did not fall below 80 mm. of Hg at any time. The patient did not pass more than 50 cc. of urine in any 24-hour period after the operation. The distal half of the right foot remained cold and cyanotic; otherwise the postoperative period was not complicated except by the anuria. He was lethargic on the seventh day after the operation, when his reflexes were hyperactive. On the eighth postoperative day he was drowsy and slept most of the time. Nine days after the operation he was hard to arouse from sleep and had slight convulsive seizures. On the 10th day of anuria he was comatose and had frequent severe convulsions and his respirations were stertorous. He was then seen by me, and arrangements for hemodialysis

were initiated, but the patient died a few minutes before dialysis was to be started, when all arrangements had been completed. The highest serum K was 6.0 mEq. per liter; the highest BUN, 110 mg/100 ml., and the lowest serum CO_2, 16 mEq. per liter. The patient was not overhydrated at any time and received a constant intravenous drip of about 600 to 800 cc. of 40% dextrose during the anuric period. His cardiovascular status was not considered to be seriously impaired on the day he died.

Comment.—This case is perhaps the most typical patient with postoperative acute renal failure. It seems reasonable to assume that his life span could have been extended if dialysis had been performed when the clinical signs and symptoms of uremia made their first appearance and were reversible. Until the very minute of his death the blood pressure was well maintained; the heart rate, slow; the rhythm, regular, and there was no cyanosis. Increasingly stertorous respiration, diaphoresis, and mounting blood pressure, all of which occurred shortly before his death, make it likely that death occurred as a result of acidosis, which could have been ameliorated by timely hemodialysis.

Comment

The role of dialysis in the treatment of acute renal failure can be defined in chemical terms only when the natural history of the disease is fully understood, which is not now the case. There is general agreement [1, 4, 9, 20, 23] that the terminal stage of acute uremia, characterized by coma, convulsions or severe cardiac failure, is not the best possible time for dialysis, even though some patients can yet be saved at this late stage by the artificial kidney. The patients presented here include approximately the same number of persons whose lives were saved by dialysis during the terminal stage as of persons who did not improve. It is not often realized but documented by the cases presented here that (*a*) terminal stages are often not reversible with or without dialysis, (*b*) preterminal stages frequently deteriorate within a matter of hours into terminal stages, and (*c*) irreversible (or slowly reversible) injury to nervous or circulatory systems can occur early (before the 10th day) in the course of acute anuria.

It has been proposed that a skilled and experienced physician is able to postpone dialysis or avoid it entirely.[1] One should receive this argument with the utmost skepticism, inasmuch as it is unsupported by evidence.

Which criteria will have to be used, then, if dialysis is to be performed before terminal changes have set in? It goes without saying that all anuric or oliguric patients, particularly those with severe injuries or infections or other protein breakdown, should have frequent electrolyte studies and that serum K levels over 7.0 mEq. per liter and blood CO_2 contents below 12 mEq. should call for immediate intensification of treatment and of watchfulness, regardless of the length of the preceding anuria. The terminal stage of acute uremia is preceded by a phase in which the patient is still responsive but shows definite nervous signs or symptoms, such as drowsiness, confusion, changes, of personality (irritability, hostility), restlessness, ankle clonus, hyperactive reflexes, slight papilledema, and edema of the retina. There are also cardiovascular signs, such as tachycardia, slight pulmonary congestion (expiratory wheezes), increased second pulmonic sound. Other signs which are frequent precursors of the terminal stage are vomiting (which should not be controlled with drugs because of the possible cumulative toxicity), retching, ileus, and persistent wrinkling of the scrotum and areola mammae. It is the appearance of these signs and symptoms which should be the indication for dialysis in uremic patients because they herald the terminal and often irreversible stage of acute uremia.

The question arises whether observation and management careful enough to comply with the criteria stated here are feasible in the average case. Experience has shown that most physicians who see only an occasional patient with acute anuria are prone to deviate from standard management even

though this is widely publicized. Even after several years of special attention to this syndrome diagnostic surprises still occur (Case 46!). I therefore favor initial hemodialysis (*a*) whenever necessary for electrolyte abnormality; (*b*) if there are any clinical signs, on the fifth day of anuria-oliguria; (*c*) if there are no clinical signs but continuing oliguria on the sixth day; (*d*) thereafter, repeat dialysis whenever indicated clinically or by serum electrolytes or by BUN over 150.

If we had adopted a rule [4] to dialyze all patients who remain anuric for five or six days, we would have dialyzed an additional six patients who recovered without the use of the artificial kidney and where this treatment would have been superfluous. We would also have dialyzed 16 of the 17 patients in whom the artificial kidney was applied too late, with an unknown and unknowable, but probably very considerable, salvage. In view of the very small risk, the conclusion is inescapable that early use of the artificial kidney would have been preferable in the present series of patients.

Summary

During the last four years 51 patients were seen or treated with acute potentially reversible anuria which was not associated with other fatal primary pathology. Thirty-four of these recovered, with or without the use of the artificial kidney. In 12 of the recovered patients the artificial kidney procedure was considered life-saving. Seventeen did not recover in spite of the potential reversibility of their renal lesions. One error which was made in the management of all 17 patients who did not recover consisted in delay in the use of the artificial kidney.

The following indications are now given for dialysis: (*a*) electrolyte abnormality (serum K above 7.0 mEq. per liter, serum CO_2 below 12 mEq.); (*b*) if there are clinical signs of uremia (as described in discussion of this paper) on the fifth day of anuria-oliguria; (*c*) if there are no clinical signs, on the sixth day of anuria-oliguria; (*d*) repeat dialysis whenever indicated clinically or by serum electrolytes or by BUN above 150 mg/100 ml.

If the above criteria for dialysis had been followed, most of the 17 patients now dead would probably have survived. Of the 34 patients who survived, only an additional 6 would have been treated with dialysis when this was not necessary for their survival.

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Addendum

Since this manuscript was accepted for publication, seven additional patients with proven acute renal failure have been seen or treated. One of these recovered without dialysis, the survival of four was attributed to the use of the artificial kidney, two died probably because dialysis was used too late (1) or considered too late (1).

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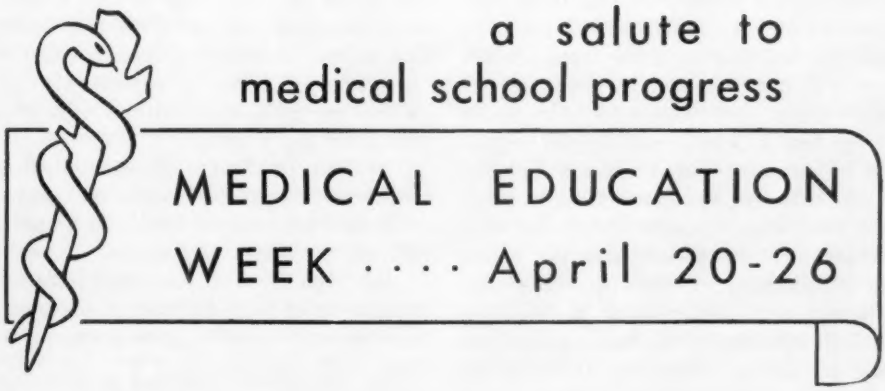

Energy Costs of Activities in Health and Disease

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For maintenance of metabolic equilibrium physical activity, like nutrition, is basic; yet, unlike the latter, interest in the relation of exercise to health and disease has been slow in developing. It is true that from the time of Hippocrates, and even before, exercise was held important for the well as for the sick, but its use was intuitive or empirical and often postulated on erroneous "systems" irreconcilable with modern scientific knowledge. Only recently have studies begun to elucidate the relationship of activity to physiologic processes. Such investigations as those of Deitrick and Keyes indicate the deleterious effect of immobilization upon calcium and nitrogen balance, circulation, and behavior.[1,2] During World War II clinicial evaluation of inactivity in convalescence led to the use of early ambulation, with consequent decrease in time of hospitalization and in incidence of secondary complications, such as pain, constipation, insomnia, and the more serious pneumonic and thromboembolic events.[3] Early and controlled application of a balanced program of rest and graded exercise demonstrated that even after a recent bout of rheumatic fever, soldiers could be returned to active duty without harm and with considerable saving of sick days.[4] There still remains to be exploited a large field in which more specific regulation of stress in chronic disease and disability is often of equal importance to drugs. Such control implies some idea of the work tolerance of the patient and the means whereby intensity of effort may be selected consonant with his tolerance, a choice requiring knowledge of the working metabolic rates of various activities. Allied to this problem is the possibility of increasing work capacity by properly chosen graded effort.

Submitted for publication Aug. 10, 1957.

The theoretical basis and methodology for the study of energy metabolism have long been established. Foreshadowed by Lavoisier's observations, in the last 50 years the law of conservation of energy has been shown to apply also to the organism. Studies by Rubner, Atwater, and others proved that when an amount of food was ingested the energy intake calculated from its heat value exactly balanced the energy output degraded into heat upon utilization in the animal body. Direct measurement of heat production in further experiments by Rubner agreed within 1% with measurements obtained from respiratory gas exchange. With the demonstration that a given O_2 uptake always yielded the same amount of energy upon utilization of a given substrate, the foundation for indirect calorimetry was laid.* It soon led to practical measurements of basal and working metabolic rates by collecting a timed sample of expired air and analyzing it for O_2 and CO_2 contents. Thus, two mutually related routes of investigation of energy metabolism in nutrition were opened. One lay in the calculation of total requirements via calorie content of the daily intake. The second involved the determination of O_2 uptake per minute to estimate the sum of total energy cost in rest and work comprising the day's routine.

The first practical application of these studies was concerned with the optimal nutritional needs in various occupations to maintain the health of workers. The value of such data is of obvious importance also in rationing of foods in times of emergency. Early attempts depended upon estimating the

* One liter of O_2 consumption is taken to be equivalent to the liberation of 5 Cal. Normally the range extends between 4.8 and 5.0 Cal., depending on the metabolic mixture. This variation represents a maximal error of 4%.

TABLE 1.—*Tailoring* *

Task	Cal./Hr.†	No. Hr.	Total Cal.
Tailoring activity	80	8	640
Dressing & undressing	33	1	33
Walking slowly	115	1	115
Sitting	15	4	60
Light exercise	85	2	170
			2,623

* 24 hr. basal rate: 37.8 Cal./hr./sq. m. × 1.77 sq. m. × 24 hr. = 1,605 Cal.
† Excess of basal.

caloric content of the food intake of persons in various occupations, but such methods are not wholly valid because of the possibility of undernutrition or overnutrition. Later the Technical Commission of the League of Nations published a category of daily food allowances for various occupations based on requirements determined in the field by indirect calorimetry.[5] Various activities during the course of the day must be known as to duration and intensity in order to arrive at the sum; in these calculations approximate values of costs for many kinds of work have been available. An example of such an accounting is given in Table 1.

Clerks expended between 2200 and 2700 Cal.; miners, 4250 Cal. daily. In a more recent analysis of various daily activities for clerks a value of 2700 Cal. was arrived at.[7] For coal miners the daily average metabolic cost was 3780 Cal. The major error in such calculations is largely due to mistakes in estimating the duration of any activity; but when carefully done a 10% approximation can be obtained. The basal rate differs little from person to person, and such variations represent a small error in daily costs. Allowances for specific dynamic action of foods are an unnecessary refinement.[7] Sleep may also influence calculation of over-all requirements. After rest the metabolism may fall below the basal, but this trend is cancelled by an increment following work or a meal. Here again the variation is small and the B. M. R. is a close enough approximation.[7]

An exception to the statement that variations in B. M. R. between persons are small applies, of course, to the adolescent. Ample evidence is available to the effect that a boy of 15 years may require calorically as much as a miner because of growth, activity, and an increased basal metabolic rate.[6]

Such investigations would be helpful in the mutually related problem of food intake and energy expenditure, particularly in an era when the effects of overnutrition and underactivity upon health are being critically examined. When the aging process is considered, basic nutritional requirements become particularly pertinent in studying atherosclerosis. Decrease in physical activity aside from work is characteristic. Besides, the fall in basal metabolism with advancing age is well documented. Dubois found in both men and women a decrease in B. M. R. of 2.5% from 20 to 50 years of age and an equal decrement by the next decade.[8] Boothby's group found a decline in men of 8% from 20 to 40 years of age and an additional one of 8% by the age of 60. In women the values were less, but at 60 years the B. M. R. was 10% below that at 20.[9] Probably the latter data are more nearly valid, based as they are upon 1467 normal persons up to ages of 68 years. Since in a sedentary type of life the basal value could easily represent 65% of the total daily expenditure, a decline of 10% in the B. M. R. without an equivalent adjustment in intake could easily lead to surplus feeding of 200 Cal., insignificant enough on a daily basis but equivalent to 150 gm. of fat deposit weekly. This exemplifies merely one of the pitfalls in attempting to study factors governing life span in humans without considering calorie intake.

There is a school of thought relying upon experiments such as those of Morris,[10] of England, that bases many ills of mankind, young and old, on activity only. It might be pointed out that these findings do not apply to such a community as Chicago.[11] What may be overlooked in drawing conclusions on "hypokinetic disease" is the fact that a laborer in England with a daily metabolic cost of 4000 Cal. may be less apt to ingest as large an excess of food because of limited budget as the clerk, businessman,

or professional, requiring some 2700 Cal. The laborer may have a smaller economic margin between enough and surfeit in England, but in Chicago he can afford a surplus of food even beyond 4000 Cal. daily. It is quite possible that sedentary habits may contribute partially, if at all, to degenerative vascular diseases; it is also probable that overnutrition in calories, fat, and protein plays a larger role, if inferences from studies on animals are valid for humans.[11-13] Another point is regard to the role of overnutrition has already been mentioned, the effect of declining B. M. R. with age. At any rate, at the present stage of knowledge of the complementary problems of nutrition and physical activity in man, sweeping generalizations regarding the role of the latter alone are not valid; the effect of the former upon atherosclerosis is far better documented.

While the main interest has pertained to the problem of optimal nutrition, energy metabolism has been used in various ways to analyze fitness and predict performance in sports. Oxygen intake rates in all-out performance appear to correlate well with the circulatory-respiratory capacity of the athlete. These tests can be readily performed on the treadmill.[14] Information of this type would be valuable for cardiac and respiratory patients; but any such stress is obviously not applicable to the clinical field. Rates of energy expenditure have also been used to predict performance required for improving records in various sports.[15]

A large area of application of energy studies lies in management of chronic cardiac and respiratory diseases in which regulation of the level of physical activity is desirable to avoid stress. In this context both duration and intensity of effort must be reckoned with. The former is readily controlled. But intensity presents difficulties because the rate of physiological work is not readily visualized by physician or patient. Advice "to take it easy" is often misconstrued and is totally inadequate because of differing opinions as to its practical meaning. Precise definition of the limit between tolerance and stress is not possible, for neither are the relevant factors fully understood nor are measurements feasible. Purely kinesiological intuition or inspection is often misleading because physiological work depends not only on the mass of active muscle but on the intensity of its contraction; the latter is not easily perceived.[16] On a practical basis judgment of intensity and duration of effort permitted must be decided upon clinical grounds. However, in considering the applicability of any specific activity the intensity of metabolic work, i. e., the energy requirement in the performance of a task, can be readily obtained by data on minute O_2 uptake. This type of determination provides a rough yardstick of general cardiovascular and respiratory work involved, as it correlates well enough with cardiac output (C. O.) and pulmonary minute ventilation (P. M. V.) within certain limits.[17,18] What these limitations are will be discussed below. At any rate, knowledge of energy cost of various tasks offers a simple means for prescribing the intensity of physical activity.

By indirect calorimetry data on costs for a wide range of activities have become available in recent years. Unfortunately, the units in which these have been expressed have not always been uniform and, probably, this confusion has contributed to the neglect among practitioners of that which may be useful in the management of chronic disease. Physiologists have used the term "metabolic units" (M. U.), by which energy expenditure is expressed in multiples of the basal rate. Thus, if the B. M. R. is 250 cc. of O_2 per minute and during a task 1000 cc. per minute are consumed, the total requirement is 4 M. U. If in this example it is desirable to assess only the cost of the work itself, then 1 M. U., that contributed by the basal metabolism, is subtracted and 3 M. U. is reported. Some publications have presented findings during activity as per cent rise rather than in metabolic units, but the concept remains the same. Thus, in the example quoted above the total cost is 400% of basal,

the working cost, 300% in excess of basal. It would appear that the former method is simpler, as it is based on integers. A practical disadvantage of any denomination in terms of the basal value is that one determination requires two experiments, the basal and working O_2 consumption. For calculation of daily food requirements from energy costs of activity, total calories per hour or calories per hour in excess of the basal value have been variously used (example above). In management of chronic disease, at least, use of a unit expressing total cost is quite justified, as one is interested in the over-all stress engendered by activity including the basal metabolism. Passmore prefers to express the expenditure as calories per minute rather than per hour, as is usually done, because activities are usually a matter of minutes and thus calculation is simplified for entire duration of work.[7] To this advantage may be added the fact that the basal amount of calories per minute is approximately unity and, hence, any figure becomes a multiple of it and readily manipulated in comparing relative total rates of activities.† Also, numerically, the M. U. is roughly equivalent to calories per minute, thus favoring easy conversion from one to the other.‡ The disadvantage of any absolute unit unrelated to B. M. R. is that it does not take into account individual metabolic differences due to sex, age, height, and weight. This shortcoming, however, is not too important for this kind of measurement where the methodical error is -10%. Furthermore, for intensities of metabolic activity rather than duration the error is not significant. In this account energy costs will be referred to as total calories per minute.

It has already been suggested that implicit in the calibration of physical activity by a scale of energy costs is the parallel relationship between rise of O_2 uptake per minute and cardiorespiratory stress. With moderate to heavy work (3.0 to 8.0 Cal. per minute and over), the increment in C. O. per liter rise of O_2 consumption per minute has been found by Fick, dye, and acetylene methods to lie between 6.0 and 6.8 liters per minute.[19-22] In terms used here, C. O. increases about 1.5 liter per rise of each calorie per minute. The correlation holds in normal and athletic subjects regardless of the position of work and state of training. For light work below 3.0 calories per minute, other factors appear to influence C. O. aside from O_2 metabolism.

In the first place, position of the limbs relative to the heart plays a decisive role in determining resting C. O. Although energy expenditure of sitting is about 15% above basal, C. O. is less by 15% to 20% because of pooling of blood in the dependent parts.[23-25] During light activity great variability was found in relating C. O. to O_2 consumption per minute. In addition to position the nature of the motor pattern and size of muscle groups appear to exert an influence.[19,23] Nevertheless, in standing activities of low intensity (1.3 to 3.0 Cal. per minute) a linear function is apparent in Grollman's data by the acetylene method, indicating a slope of 2.0 liters of C. O. per unit of caloric expenditure.[19] When plotted against calories per minute, values of C. O. obtained by the direct Fick method on normal subjects working a bicycle at metabolic rates of 2.0 to 4.0 Cal. per minute give a ratio of 1.9, whether sitting or recumbent.[26,27] On the other hand, no such correspondence was found by the same method with employment of normals working in the supine position at these low rates.[28] When mitral stenosis and chronic pulmonary disease are considered, although C. O. rises, great variability was found in 18 patients at metabolic rates up to 5 Cal. per minute.[26,28]

In effect, then, energy costs can serve as an index for cardiac output, particularly in moderate to heavy activity. The increment in C. O. during light tasks in patients

† This fact is purely fortuitous and, though only approximately correct, is useful for clinical purposes. Thus between ages 20 to 60 for a wide range of heights and weights, the B. M. R. for males is 1.1 to 1.3 Cal. per minute, for females, 0.9 to 1.1 Cal. per minute.

‡ Not true for high values.

with mitral stenosis and chronic pulmonary disease is not as predictable, but the absolute change is small and consistent clinically with the small increase in O_2 uptake, particularly in the sitting position. As Kottke points out, sitting rather than reclining at a 45-degree angle with knees bent is the basal position for patients from the viewpoint of cardiac work. Light hand activities done while sitting impose no more stress than this favorite hospital position in bed.[22]

But the crucial physiological function in deciding the validity of the energy cost scale is the relationship of this factor to cardiac work, i. e., the product of C. O. and peripheral resistance. Investigations in normals have shown that left ventricular work is increased less than two times with energy expenditures of 2 to 3 Cal. per minute and with 4 to 6 Cal. per minute, a twofold to fourfold increase appears.[22,26,27] In cardiac and pulmonary disability this trend is not apparent, as might be expected. However, for metabolic costs of 2 to 5 Cal. per minute left ventricular work rises 1.5 times of resting; right heart work doubles.[26,28] Thus, at practical levels of effort the cardiorespiratory patient undergoes an increase in stress illustrated by the Fick method. Ballistocardiographic findings must be accepted with caution in this regard. For example, one study on climbing stairs (9 to 14 Cal. per minute) revealed only a rise of 1.8 times in C. O. and cardiac work.[29] This finding is not in accord with direct measurements of hemodynamics. As pointed out by Brown and co-workers, exercise often produces artifacts in recording due to increased amplitude and rate of excursion of the thoracic cage.[30] Abnormal ballistocardiograms, also, make interpretations doubtful.

Oxygen consumption per minute and P. M. V. in a given person fall nicely into a straight line function, barring hyperventilation due to anxiety, obstruction, and the like. This correlation is so reliable that it has been suggested that O_2 consumption per minute for a large number of activities may easily be found for any one person by setting up a regression line on the basis of five actual determinations and then interpolating values for working metabolic rate from found P. M. V.[31] This procedure is reliable in P. M. V. between 15 and 50 liters per minute.

Another effect of exercise is to increase the blood flow in the pulmonary vascular bed.[26-28] This feature may be undesirable in active pulmonary tuberculosis, thus suggesting another reason for regulating physical effort.

Energy Costs of Self-Care Activities

Regulation of physical activity may, then, be predicated upon O_2 requirements as a first approximation. In the hospital the physician resorts to classifications of physical activity to grade stress in the management of tuberculosis and myocardial infarction, for it is widely accepted that untimely and uncontrolled activity may adversely influence the course of events. In spite of the widespread use of this principle, its application is intuitive rather than based on data of the metabolic work inherent in various routines of daily life. Such data, some of which appear in Table 2, are now abundantly available in the English language for such activities as lying, sitting, dressing, conversing, walking, and many others.[7,32] Three investigations are of enough importance to hospital practice to bear mentioning.

In sitting, cardiac output is less than in the supine or reclining positions (see above). This fact is at the basis of the chair treatment of myocardial infarction.[33] It must be realized, however, that in the act of moving from bed to chair there are transient rises

TABLE 2.—*Self-Care Activities*

Activity	Cost, Cal./Min.	Activity	Cost, Cal./Min.
Rest, supine	1.0	Walking, 2.5 mph	3.6
Sitting	1.2	Showering	4.2
Standing relaxed	1.4	Using bedpan	4.7
Eating	1.4	Walking downstairs	5.2
Conversation	1.4	Walking, 3.75 mph	5.6
Dressing, undressing	2.3	Propulsion, wheelchair	2.4
Washing hands, face	2.5	Ambulation, braces & crutches	8.0
Bedside commode	3.6		

in cardiovascular (and metabolic) work to undesirable levels.[23] The method of management must circumvent undesirable effort by putting means at the disposal of the patient to lift him in and out of the chair.

A practice of questionable value in furthering rest in seriously ill patients is indicated by a study on the use of the bedpan.[34] For both normal subjects and cardiac patients energy costs for bedside commode and bedpan were found to be 3.6 and 4.7 Cal. per minute, respectively. The former value even included the activity associated with getting out and back to bed. Although during this phase significant rises in cardiac output probably occurred, though momentarily,[23] the main increase in energy cost and, hence, stress was due to the unnatural position upon the bedpan. This important research lends weight to the complaint that bedpan toileting is fatiguing.

Another self-care routine prescribed with little thought of the possible stress is showering. Itemizations of specific activities in a graded program as practiced in tuberculosis sanitoria usually allow showering when other activities of lower cost are interdicted. Studies comprising 3 healthy and 11 convalescent tuberculous subjects yielded an average value of 4.2 Cal. per minute as the energy expenditure in showering.[16,32] Values for normal persons fell well within the range found for patients. The magnitude of metabolic rate may be a source of some surprise, but attention is called to the fact that all muscles of the body are utilized in balancing, bending, and reaching. Further validity of the findings comes from the fact that O_2 debts of 0.7 to 1.5 liters were contracted in three to four minutes. These studies are a further confirmation of the fact that inspection can not supersede measurements in gauging stress of activity.

Energy Costs of Walking

Numerous investigations have appeared illustrating the influence upon energy costs of walking of such variables as weight, speed, incline, and terrain. These have been correlated by Passmore and Durnin.[7] Cost rises with obesity in a linear fashion at a constant rate of speed but in an exponential fashion with increasing rates of walking and steeper grades. Thus, at 2.5 mph a person weighing 160 lb. uses 3.8 Cal. per minute; at the military rate of 3.75 mph, 5.4 Cal. per minute; at 5.0 mph, 8.2 Cal. per minute. On a 5% and 15% grade the costs for the same person at 2.5 mph are 5.5 Cal. per minute and 8.7 Cal. per minute, respectively. From the point of view of energy metabolism, and presumably stress, a walk on level ground at 3.75 mph is equivalent to an uphill pull on a 5% incline at 2.5 mph. Rough terrain like a ploughed field compared with a smooth level imposes a further price increase of 40%.

Another incline one normally negotiates is stairs. Sherman gives the high value of 14.3 Cal. per minute for climbing stairs and 4.2 Cal. per minute for going downstairs.[35] Passmore's figures for ascent are probably equivalent: about 10 Cal. per minute for a 75 kg. man moving at a vertical speed of about 50 ft. per minute. This activity requires the highest intensity of all routine activities encountered, and yet in some tuberculosis sanitoria this fact is neglected, even though a rigid activity classification is enforced. While climbing stairs is of brief duration, a short intense burst of physical effort may conceivably exceed a critical level at which pathological changes may be induced.

Energy Costs in Occupational Therapy

In hospitals caring for prolonged illness like tuberculosis, the occupational form of therapeutic activity is in wide use to improve work capacity gradually. It may be brought to the bedside, or the patient, when able, may go to the shop. It is, naturally, of concern to the physician how much effort at what intensity should be allowed. A wide selection with associated energy costs is at his disposal.[7,16,32,36] As previously mentioned, reclining O_2 consumption is less than sitting, but attention is drawn to the fact

TABLE 3.—*Occupational Therapy Activities*

Task	Cost, Cal./Min.	Task	Cost, Cal./Min.
Leather punching & lacing, reclining	1.2	Copper tooling	1.6
Leather tooling, reclining	1.2	Bookbinding, light	1.6, 1.9
Making link belt, reclining	1.3	Leather carving, sitting	1.8
Rug hooking, sitting	1.3	Typing, rapidly	1.8
Chip carving, reclining	1.5	Weaving, floor loom	2.0
Knitting (23 stitches/min.)	1.5	Chisel carving with mallet, standing	2.0
Weaving, table loom	1.5, 1.8	Chisel carving without mallet, sitting	2.2

TABLE 4.—*Industrial Activities*

Task	Cost, Cal./Min.	Task	Cost, Cal./Min.
Watch repairing	1.6	Carpentry	6.8
Armature winding	2.2	Binding sheaves	7.3
Radio assembly	2.7	Mowing lawn by hand	7.7
Sewing at machine	2.9	Felling tree	8.0
Cobbling	3.0	Shoveling	8.5
Bricklaying	4.0	Ascending stairs,	
Plastering	4.1	17 lb. load, 27 ft./min.	9.0
Tractor ploughing	4.2	Planing	9.1
Wheeling barrow		Tending furnace	10.2
115 lbs; 2.5 mph	5.0	Ascending stairs,	
Horse ploughing	5.9	22 lb. load, 54 ft./min.	16.2

that the latter position is the more desirable to minimize stress according to the findings on cardiac output.[23-25] It may be further pointed out that in 24-hour-a-day bed rest, if conversation is allowed (1.4 Cal. per minute), then occupational therapy activities of similar magnitude may be allowed in selected patients. Some of these are rug hooking (1.3 Cal. per minute), leather tooling (1.2 Cal. per minute), drawing (1.5 Cal. per minute). Overly severe restriction, although apparently erring on the safe side, brings in its train undesirable psychological reactions[1] which of themselves also increase O_2 consumption and cardiac output.[19] Table 3 presents some examples of these activities.

Energy Costs in Industry

For the cardiac or pulmonary cripple vocational rehabilitation rests upon the physiological requisite of cardiorespiratory ability. Control of occupational activity in the "apparently arrested" tuberculous patient aims at a rate well below the actual reserve upon discharge. In either case metabolic demand during work is kept relatively low; and the mutually related problems of selective placement, choice of suitable activities, and application of work simplification principles are geared to achieve regulation of energy expenditure.

It is true that there is no clinical method to determine accurately the work capacity of the heart. It is equally true that it is difficult to know the changes in stress imposed by varying conditions of life. However, there are available now extensive data on energy costs in a wide variety of occupations, upon which the physician can base a reasonable attempt at approximate control of activity (Table 4). If metabolic demand is roughly proportional to cardiac work (except for the reverse relationship between O_2 consumption per minute and C. O. in lying and sitting), then the former can serve as a guide to the selection of activities designed to minimize cardiovascular or respiratory stress. As a simple procedure the physician can determine that activity of maximum intensity performed for five minutes which is without discomfort to a patient, i. e., without dyspnea, palpitation, angina, or cyanosis. Knowing its energy cost (for example, walking 2.5 mph, 3.6 Cal. per minute) he may safely choose other activities in a similar range, provided effort is punctuated by pauses. More elaborate tests have been detailed.§ It is also suggested that the cardiac classification as used at present be made more specific by assigning to each therapeutic class an appropriate range of values of energy costs when considering vocation.

In order to do this, some form of continuum from light to severe work in semiquantitative terms must be developed. This type of grading is most conventiently supplied by the concept of metabolic cost. How can one correlate this gradation with that of the widely used therapeutic cardiac classification in considering employment? It will be noted that the crux of the current classification is "ordinary activity." In this context

§ Recently Ford and Hellerstein have published the energy cost of the Master two-step test (8.5 Cal. per minute), and suggested methods of utilizing the test to determine the tolerance of cardiac patients (*J. A. M. A.* 164:1868, 1957).

"ordinary" means that activity done by the majority of workers, rather than activity for a particular person, say, a lumberman. It is likely, moreover, that a metabolic demand of 5 Cal. per minute represents activity impossible to perform continuously for eight hours without interpolated periods of rest.[37] This level is equivalent to an O_2 uptake of 1.0 to 1.25 liters per minute and could represent the upper limit for Class A. Exceptions to this standard may be individualized. A minute O_2 uptake of 500 to 600 cc., 2.5 Cal. per minute, may be taken as "ordinary."[7] Therefore, for the purposes of guidance in the type of job allowed, one may have the following gradation:

Therapeutic cardiac classification for continuous activity:

Class A—no restriction; metabolic cost up to 5 Cal. per minute

Class B—no restriction of ordinary activity; metabolic cost up to 2.5 Cal. per minute

Class C—moderate restriction of ordinary activity; metabolic cost up to 2.0 Cal. per minute

Class D—patients would not be candidates for vocational rehabilitation, but an expenditure of 1.5 Cal. per minute for any considerable period may be the limiting boundary

The energy limitations in B and C would still permit a wide selection of semisedentary employment in office work, light engineering, draufting, and many other fields. It is emphasized that this plan refers only to continuous activity.

Grading of metabolic demands for healthy workers is a different matter. While no worker can maintain an expenditure of 5 Cal. per minute for eight hours, there are many occupations where rates are much higher, as they are punctuated by rest. Christensen has suggested the classification of grades of occupation by magnitude of cost[38] shown in Table 5.

TABLE 5.—*Grade of Occupation by Magnitude of Cost*

Grade	Cal./Min.	Example
Light	2.6-4.9	Mixing cement
Moderate	5.0-7.5	Beating rugs
Heavy	7.6-10.0	Splitting wood
Very heavy	10.1-12.5	Slag removal
Extraordinarily heavy	12.5 & up	Carrying 60 lb. upstairs

These are average figures subject to variations in individual persons, but at least they are physiological expressions of a nomenclature in industry heretofore vague and unrealistic. Obviously, the higher figures do not form the basis of continuous daily output but rather peaks of stress in the work day. Light work is one which may be performed without pause.

It is of interest to compare this Table with data from a similar one published in a League of Nations report over 20 years ago[5]:

Grade	Cal./Min.
Light	Up to 2.6
Moderate	2.7-3.8
Hard	3.9-6.3
Very hard	6.4-up

Christensen's grading is about twice as high at that formulated by the League of Nations for similar categories. The disparity between these two considered opinions is not explained by changing concepts of work. It would appear that the former Table is based upon the practical realization that many industrial activities are performed in interrupted fashion and an assessment of peak load is desirable. The League's Table appears to be based on gradations of intensities that can be more or less continuously maintained. It has already been stated that 5 Cal. per minute appears to be the ceiling for this quality of performance.[37] Actually, most occupations are episodic in performance and, therefore, Christensen's classification is the more realistic.

Energy Costs of Domestic Activities

Because many household tasks fall in the range of moderate to heavy work for normal people, consideration of housekeeping finds a legitimate place in rehabilitation of the housewife disabled by cardiac, respiratory, or neuromuscular disease. Time-saving and work-planning principles serve to reduce metabolic demand. Modern labor-saving devices further cut down energy costs, but they may not be within the reach of all who need control of physical stress. Good rehabilita-

TABLE 6.—*Housework Tasks*

Task	Cost, Cal./Min.	Task	Cost, Cal./Min.
Hand sewing	1.4	Scrubbing floors	3.6
Sweeping floor	1.7	Cleaning windows	3.7
Machine sewing	1.8	Making beds	3.9
Polishing furniture	2.4	Ironing, standing	4.2
Peeling potatoes	2.9	Mopping	4.2
Scrubbing, standing	2.9	Wringing by hand	4.4
Washing small clothes	3.0	Hanging wash	4.5
Kneading dough	3.3	Beating carpets	4.9

tive procedure should include specific advice against those activities at variance with their presumed functional capacity. While in the case of many cardiacs activity would be prohibitive for tasks labeled in Christensen's classification as light (2.6 to 4.9 Cal. per minute), these will not be beyond many housewives' reserve capacity for brief periods. An extensive listing of energy demands for housekeeping is within reach [7] and may be used in conjunction with the cardiac work classification herein suggested. Data appear in Table 6.

Energy Costs of Calisthenics

Regulation of physical activity may be advisable in convalescence when "deconditioning" prevails. Deconditioning may be defined as that state when, after confinement to bed, deterioration of cardiovascular, respiratory, neuromuscular, and other physiological functions temporarily renders the person unfit for physical activities ordinarily undertaken without difficulty. In short-lived acute medical or surgical illnesses, early progressive ambulation is adequate in reversing this state without a more specific exercise program. In convalescence after myocardial infarction or rheumatic heart disease, loosely controlled activity may be unwise. Mention has already been made of a carefully applied program of calisthenics in military wards. As a guide a table of costs for 42 calisthenic exercises has been constructed by Weiss and Karpovich [39] from measurements by indirect calorimetry on one well-trained subject. The costs ranged from 2 to 10 Cal. per minute and included the recovery O_2 consumption (O_2 debt). They would probably be higher for untrained convalescents at the outset.

Less well known is the fact that passive motion is accompanied by increases in O_2 uptake. Bahnson and co-workers caused feet, legs, and thighs of subjects to be moved passively while they were seated on a motorized bicycle.[40] The changes ranged from 16% to 58% above the resting seated values. Before these results can be accepted, it must be clarified whether unintentional voluntary contractions of the limbs and, particularly, postural activity of the trunk were responsible for the rise in O_2 metabolism. Regardless of the mechanism this fact places passive exercise at the beginning of a graded program.

Energy Costs of Sports and Recreation

For the sound the considerations of energy costs of sports and recreation are of no import, but it is interesting that recreational effort often exceeds occupational effort. Clinically, the physician is often faced with the practical question of advising suitable recreation for a person recovered, for example, from myocardial infarct. It may be of some surprise to a golf enthusiast that the rate of work in this sport is 5 Cal. per minute. Walking uphill and the grassy terrain tend to elevate the cost. The average rate and total expenditure could be smaller provided the person walked slowly and paused frequently. Examples of continuous activity that may be contraindicated in cardiorespiratory disability or tuberculosis are trotting (8.0 Cal. per minute), galloping (10.0 Cal. per minute), swimming 60 yd. per minute (5.0 Cal.). Many other sports

TABLE 7.—*Recreational Activities*

Activity	Cost, Cal./Min.	Activity	Cost, Cal./Min.
Painting, sitting	2.0	Swimming, 20 yd./min.	5.0
Playing piano	2.5	Dancing	5.5
Driving car	2.8	Gardening	5.6
Canoeing, 2.5 mph	3.0	Tennis	7.1
Horseback riding, slow	3.0	Trotting horse	8.0
Volley ball	3.5	Spading	8.6
Bowling	4.4	Skiing	9.9
Cycling, 5.5 mph	4.5	Squash	10.2
Golfing	5.0	Cycling, 13 mph	11.0

are listed in the literature.[7] Table 7 gives some examples. As pointed out, walking can be unsuspectingly high in stress, and, if this form of exercise is prescribed for a convalescing tuberculous patient, for the sake of consistency he should be made familiar with the allowed rate of walking. Patients with pulmonary insufficiency or limited cardiac reserve need no such instruction, as dyspnea acts as an effective check.

Energy Costs of Activities in Disability

In this context disability of the locomotor apparatus is meant, rather than the hidden disabilities of reduced cardiac and respiratory functions already discussed. Few data are available on the metabolic work required except for amputees, ambulation with crutches, and propelling a wheelchair. The expenditure per minute in the last activity found in three healthy subjects moving on level ground at 105 ft. per minute (1.2 mph) was 2.4 Cal., just about light work, industrially speaking.[32] The requirement of ambulation in paraplegics by a swing-through gait || was enormous in many cases, considering the relatively small remaining active muscle mass of the upper extremities.[41,42] At rates ranging from 88 to 282 ft. per minute (1.0 to 3.2 mph), energy costs were found to be at least 3.5 to 8.0 Cal. per minute, respectively. Sustained ambulation for practical distances was impossible at metabolic levels of 5 to 6 Cal. per minute. The determinants producing grossly inefficient muscular work and thus militating against prolonged ambulation were loss of trunk muscles, particularly extensors above L-1, involvement of respiratory muscles, impairment of upper extremities, and advancing age. Along with energy expenditures of 5 Cal. per minute or over there were noted maximal O_2 debts contracted within four minutes, maximal O_2 uptakes per minute, lactacidemia up to 70 mg. per 100 cc., and pulse rates of 130 to 150. For many, metabolically speaking, ambulation for four minutes compared with a 400-yard dash for normal man. The swing-through gait is inherently inefficient; the mechanical efficiency was estimated as 4% to 6%. The conclusions reached are of interest to the field of rehabilitation:

> Ambulation for some paraplegics as a usual means of progression is impractical, as it involves severe physiological stress and can not be maintained to cover significant distances. . . . This restriction does not preclude standing and walking short distances merely for self-care or as an exercise to maintain physiological balance. . . . For the severely involved, it is more constructive to devote the bulk of time to vocational training in a wheelchair. . . .

It is of some theoretical interest that the B. M. R. in 11 paraplegics, in spite of the reduced surface area particularly in patients with residua of poliomyelitis, averaged −2% of the predicted value. Values ranged from +11% to −14%; eight subjects ranged from +7% to −4%.[41]

For those paraplegics paying large metabolic prices during ambulation, the actual pulse rates were far in excess of those predicted from the corresponding O_2 uptakes per minute, with use of curves relating these two factors in normal men during physical activity.[20] Cardiac output by inference from the same curves was one and one-half to two times lower as a function of the determined O_2 uptakes than of the found pulse rates. The lower value for C. O. is probably the correct one in view of the reduced active muscle mass. Thus, combination of high pulse rate and small cardiac output presupposes a small stroke volume as well as a reduced circulating blood volume. These suppositions await further work in an untouched field, circulatory dynamics in and adjustments to neuromuscular disabilities.

The affect of more or less bracing upon energy requirements was also explored.[41] Cost was reduced by 1 Cal. per minute in a paraplegic patient when using a Knight spinal ¶ with long leg braces and pelvic band as compared to absence of the trunk support. In comparing two other similarly impaired paraplegics, one with the addition of a spinal

|| The braced legs swing forward in an arc beyond the crutches, which are then advanced to check the forward motion of the body.

¶ Brace for trunk support.

brace to standard bracing appeared to benefit by the fact that expenditure during ambulation was lower.[43] The differences of opinion between the schools of maximal and minimal bracing may be resolved by studies such as these.

Muller determined O_2 consumption in amputees.[44] Unilateral above-knee amputees walking on level ground with a monaxial knee joint required 25% more energy expenditure than normal subjects at the same speed. Efficiency of work was higher with this type of joint than with more elaborate polyaxial joints with braking mechanisms. Such studies in hemiplegics would also be useful in correlating physical activity with tolerance and efficiency.

Summary

A review of the use of energy costs of various activities in health and disease brings out the fact that this field of physiology has so far had major application to the field of nutrition. Inasmuch as O_2 uptake per minute is an approximately good index of cardiorespiratory stress and this metabolic measurement is relatively simple and accurate enough for clinical use, calibration of activities is possible in terms of energy expended. Those interested in regulating physical stress in chronic cardiac and pulmonary disease and in convalescence from acute serious disease have availabe a method for prescription in relation to industry, the home, recreation, and exercise. Energy-cost studies may also be applied to the correlation of residual capacity with various demands of daily living in the orthopedically disabled.

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The Use of Diphenylhydantoin (Dilantin) Sodium in the Treatment of Ventricular Tachycardia

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Ventricular tachycardia, which appears in about 2% of the cases, is admitted to be a serious complication of acute myocardial infarction. It most commonly occurs within the first five days but may occur later during the course of the disease, particularly in those patients who have been given digitalis.[1] Spontaneous reversion to a normal sinus mechanism is rare, and it is therefore a situation which calls for prompt, exact diagnosis and therapy.

Sabathie[2] has reported the treatment of ventricular tachycardia with morphine sulfate. It has been suggested by Gold[3] that other central nervous system depressants, particularly barbiturates and bromides, might be used for the treatment of ventricular ectopic beats. Harris,[4] noting that the heart and central nervous system respond to many drugs in a similar fashion, reported that diphenylhydantoin (Dilantin) sodium caused cessation of ventricular ectopic activity, produced by ligating the anterior descending coronary artery in dogs. This same author has additionally noted[5,6] that other agents, including procaine amide hydrochloride, are effective in their antiarrhythmic activity.

Procainamide (Pronestyl) hydrochloride is now the drug of choice for ventricular tachycardia. It may be given orally, intramuscularly, or, in critical situations, intravenously. The current concept of intravenous therapy entails the simultaneous use of arterenol, to avoid the hypotensive effects of procainamide. In addition, agranulocytosis,[7] chills and fever,[8] ventricular fibrillation,[9] ventricular acceleration,[10] convulsions,[11] and nausea and vomiting have been reported. Generally, these toxic manifestations are felt to be infrequent, and the drug is considered relatively safe when properly administered.

More recently, Mosey[12] compared the activity of diphenylhydantoin sodium, procaine hydrochloride, procainamide hydrochloride, and quinidine hydrochloride and found them qualitatively similar in abolishing the ventricular tachycardia resulting from ouabain overdosage in unanesthetized dogs. No mechanism of activity was advanced, but the author has suggested that diphenylhydantoin sodium might prove clinically useful in counteracting ventricular hyperirritability. On the basis of this work, diphenylhydantoin sodium was used intravenously in the following case, as a treatment for ventricular tachycardia.

Report of Case

A 42-year-old white male office worker was admitted with a history of nausea, vomiting, and profuse diarrhea and severe epigastric pain of approximately 18 hours' duration. This had followed rather strenuous physical activity, which was not in excess of what had been his habit. Both the maternal and the paternal family history revealed an inordinately high incidence of vascular disease. His father had died at the age of 43 with an acute myocardial infarction, and his mother has marked hypertensive arteriosclerotic heart disease and a history of previous myocardial infarction.

The patient had been known to have marked hypertension in the past, and approximately 10 years previously a Smithwick sympathectomy had been suggested but was refused by the patient. Since that time he had been relatively asymptomatic, and his medical attention, sparse.

Physical examination revealed a rather lean asthenic male, ashen in color, moderately apprehensive, and complaining of precordial discomfort radiating into both arms. The respirations were slightly labored, and the blood pressure,

Submitted for publication Aug. 16, 1957.

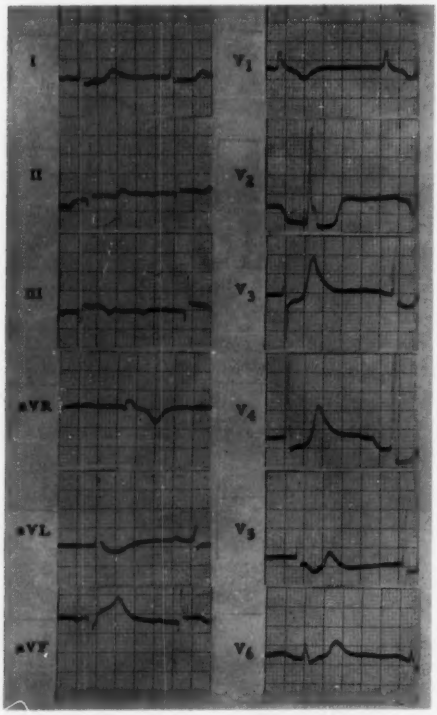

Figure 1

178/100 in both arms. The fundi revealed Grade II atherosclerotic change. The heart was moderately enlarged to the left, and a normal sinus mechanism with an apical rate of 70 was present. No murmur was heard, and the pulmonary fields were clear. The liver and spleen were not palpably enlarged. The femoral pulsations were present and forceful. No peripheral edema was noted.

The initial cardiogram (Fig. 1) revealed the changes consistent with a posterior myocardial infarction, multiple premature beats, and a complete heart block. The serum glutamic oxalacetic transaminase level was 158 Sigma-Frankel units. The white blood cell count was 17,500, with 91% polymorphonuclear cells.

The patient was treated in the accepted fashion, with bed rest, sedation, oxygen, and anticoagulant therapy. On the eighth hospital day the complete heart block had disappeared and a normal sinus mechanism was present without premature beats (Fig. 2). His general situation appeared to be satisfactory. Because of some clinical premature beats, procainamide, in a dose of 250 mg. every eight hours, was started on the 10th day. The patient experienced a sensation of heaviness in the precordium upon awakening on his 13th hospital day; the apical rate was found to be 160, grossly irregular, and the blood pressure, 170/70. A cardiogram taken at this time (Fig. 3) revealed a complete heart block with paroxysms of ventricular tachycardia. The dose of procainamide was increased to 250 mg. every four hours. This situation persisted until the following day, when 3 grains (0.19 gm.) of quinidine was added to the oral dose of procainamide, given every four hours, and a single intravenous dose of 250 mg. of procainamide was given.

The patient was seen in consultation at this time and found gravely ill, with cardiographic findings of typical ventricular tachycardia (Fig. 4). In spite of the previous history of complete heart block, it was felt that intravenous procainamide, if carefully controlled, was the treatment of choice. The patient was in profound shock, although the blood pressure was 110/70. With a constantly regulated drip of arterenol in 10% Travert (invert sugar) in water, continuous electrocardiographic monitoring, and a cardiac pacemaker-defibrillator in place, procainamide was given intravenously. During a period of approximately two hours, 2300 mg. of procainamide was given, in spite of several episodes of marked hypotension, but finally discontinued because of disturbing widening of the QRS complex without reversion to a normal sinus mechanism. The patient's condition remained dis-

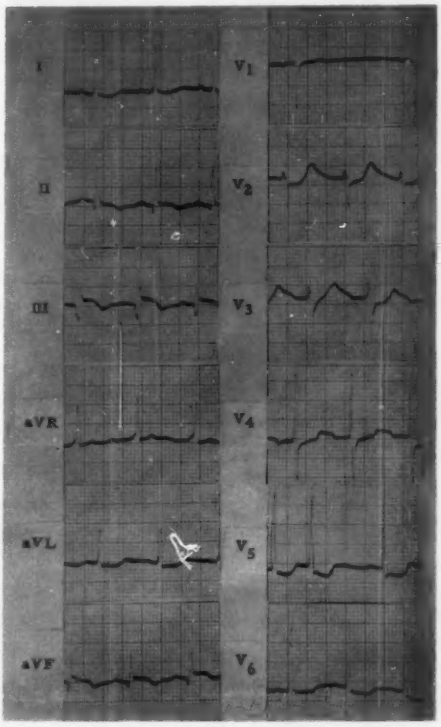

Figure 2

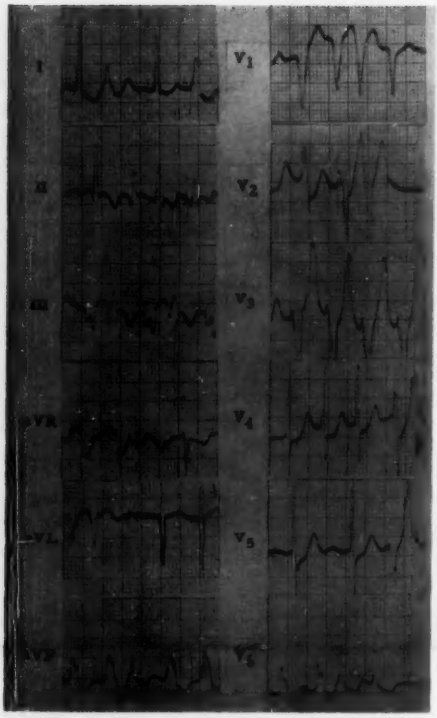

Figure 3

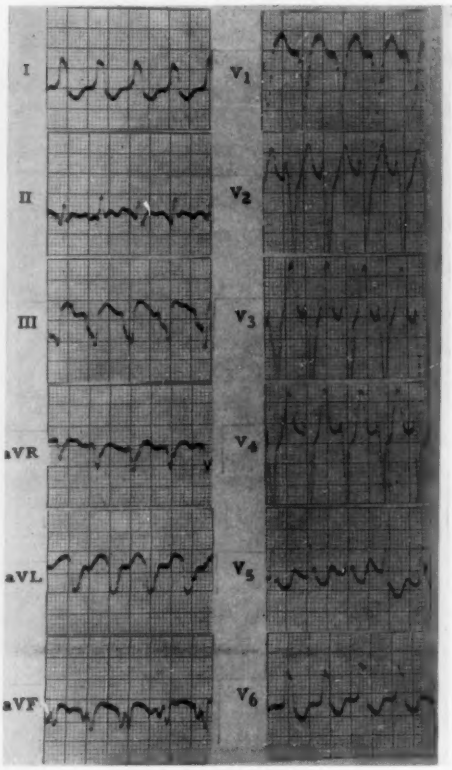

Figure 4

turbingly critical, and it was considered advisable to investigate the therepeutic potential of intravenous diphenylhydantoin sodium. This drug was administered slowly intravenously in a dose of 250 mg. while the constant infusion of arterenol was maintained. Severe, painful, but transient burning of the extremity, associated with minimal drowsiness and a sensation of floating, ensued. A cardiogram recorded approximately two minutes later (Fig. 5) revealed a normal sinus mechanism coupled with premature auricular contractions. In 20 minutes ventricular tachycardia had recurred. An immediate additional dose of 250 mg. of diphenylhydantoin sodium was given, and within moments a normal sinus mechanism appeared (Fig. 6). Four hours later ventricular tachycardia returned and was again successfully reverted to a normal sinus rhythm with 250 mg. of intravenous diphenylhydantoin sodium. Because the duration of effectiveness of diphenylhydantoin sodium was unknown, a constant, slow intravenous infusion of 250 mg. of diphenylhydantoin sodium in one liter of 10% Travert and water was started. The normal sinus mechanism was maintained in this fashion for successive periods of six and four hours. At these intervals ventricular tachycardia returned but was

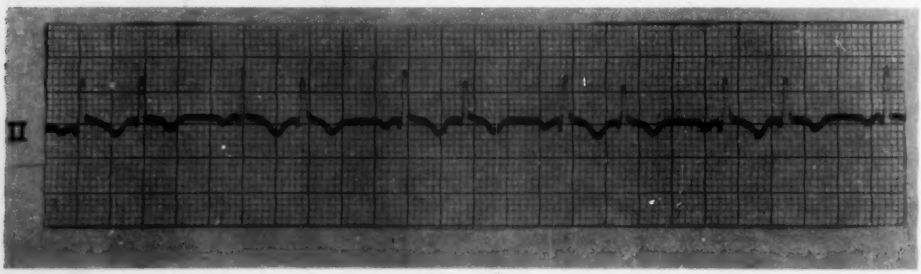

Figure 5

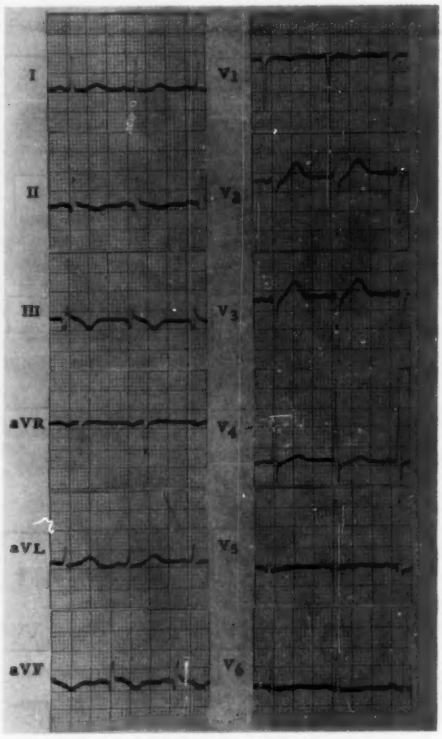

Figure 6

promptly reverted with additional intravenous doses of 250 mg. of diphenylhydantoin sodium. At this time it was considered advisable to supplement the intravenous therapy with 3 grains of diphenylhydantoin and 500 mg. of procainamide every four hours orally. Eighteen hours after its initiation the intravenous infusion of diphenylhydantoin sodium was discontinued. An electrocardiogram at this time showed the previously described posterior myocardial infarction with a normal sinus mechanism. On the following day procainamide was discontinued, and the patient was maintained with 3 grains of diphenylhydantoin orally every six hours. There was no recurrence of signs of ventricular irritability, and the patient made an uneventful recovery.

Comment

A case of ventricular tachycardia complicating a posterior myocardial infarction of the 13th postocclusion day is presented. The serious disturbance of rhythm was apparently refractory to the presently favored treatment with procainamide hydrochloride but responded to diphenylhydantoin sodium.

It would appear that diphenylhydantoin sodium administered intravenously may represent a drug with a wide margin of safety which will effectively control serious ventricular hyperirritability as manifested by ventricular tachycardia. The drug has been previously reported as being experimentally comparable with procaine hydrochloride and procainamide hydrochloride, but this is felt to be the initial report of its clinical application in the therapy of ventricular tachycardia complicating myocardial infarction. The proper technique of administration, the duration and mode of action, and its possible oral usefulness are but a few of the considerations which deserve further clinical clarification.

Summary

A case of ventricular tachycardia complicating myocardial infarction is presented which was successfully treated with intravenously administered diphenylhydantoin (Dilantin) sodium.

Further investigation is suggested to ascertain the true clinical value of the drug.

239 I. O. O. F. Building.

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Parietal Pleural Needle Biopsy

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Introduction

Pleural effusion is a common diagnostic problem. Many times an etiologic cause is immediately evident; however, in the remaining cases the physician may have to resort to all available methods, including thoracotomy, to arrive at a satisfactory solution. The purpose of this paper is to present the results of needle biopsy of the parietal pleura and to compare it with information obtained by other methods.

Method

Needle biopsy of the parietal pleura was performed with use of a Vim-Silverman biopsy needle, as first reported in 1955, by DeFrancis, Klosk, and Albano.[1] Bleeding, clotting, and prothrombin times were routinely determined to rule out any coagulation defects prior to biopsy. After the biopsy site was selected by x-ray and physical examination, the skin was sterilized with thimerosal (Tincture Merthiolate). The patient was placed in a sitting position and 1% procaine hydrochloride was used to infiltrate the skin, intercostal muscle, and parietal pleura. A skin incision of a few millimeters was made with a Bard-Parker blade in the center of the skin wheal. A 20 gauge needle with a syringe attached was inserted into the interspace along the upper margin of the lower rib until fluid was obtained. The needle was then slowly withdrawn, with constant suction being maintained until the free flow of the fluid stopped. A sterile Kelly clamp was applied to the needle flush with the skin, and both were withdrawn. The distance from the point of the needle to the Kelly clamp was measured on a Vim-Silverman needle, and the biopsy needle was then inserted through the skin incision to the distance indicated by the clamp. The clamp was removed, the biopsy shaft was inserted all the way, and the outer needle was advanced approximately 2 cm. while the biopsy needle was held in place. Both needles were completely rotated in opposite directions and withdrawn together. As did Heller et al.[2] and Katz et al.,[3] I later modified this original method in two ways. First, if fluid was not present, the biopsy needle was inserted until pleural resistance was felt and the biopsy needle was then advanced. Second, in the later biopsies, the direction of the needle was varied to obtain two or three specimens through the same incision. After the biopsy specimen was obtained, a thoracentesis was performed through the already anesthetized site.

Submitted for publication July 6, 1957.

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Material

The 17 cases in this series were all from the University of Oklahoma Medical Center. Ages ranged from 17 to 78 years, with the majority, or 14 patients, being over 50 years of age. There were 12 females and 5 males. The patients were selected because they either presented pleural effusion as a diagnostic problem or there was a high suspicion of neoplasm or tuberculosis, and the hope was to obtain a tissue diagnosis before therapy was instituted. Biopsies were not done in cases obviously secondary to pneumonia, cardiac failure, and renal disease.

When possible, information was obtained about protein, cell count, microscopic examination of cell block for malignant cells, cytology, and cultures of pleural fluid. The cell blocks were prepared by making sections from paraffin blocks of the centrifuged sediment from the pleural effusion. These were reported in one of four ways: negative, inflammatory, hemorrhagic, or malignant cells. The cytologic examinations were done with use of Papanicolaou's method and reported with use of his criteria of malignancy[4]: Class I, absence of atypical or abnormal cells; Class II, atypical cells present but without abnormal features; Class III, cells with abnormal features suggestive but not conclusive for malignancy; Class IV, cells and cell clusters fairly conclusive for malignancy; Class V, cells and cell clusters conclusive for malignancy. Histologic diagnosis of pleural needle biopsies were divided into four categories: neoplastic, caseating granuloma, fibrosis, and insufficient specimen.[2]

Results

The pertinent data are presented in Table 1. Fourteen of the seventeen patients

TABLE 1.—*Studies in Fourteen Patients with Neoplasms*

Diagnosis	Pleural Biopsy	Cell Block	Cytology Class IV-V
Positive	10	6	5
Negative	4	3	4
Not done	0	5	5
Total patients	14	14	14

in this series were proven to have neoplastic involvement of the pleura. In nine of these biopsies were done only once, and in one patient biopsy was done twice. In the remaining four cases with malignancy, five biopsies were performed; four of these were reported as insufficient material, and one, as chronic pleuritis. There were 15 cell-block examinations on the pleural fluid of nine of these patients with malignancies, with six of the patients having at least one positive report. In addition, there were 14 cytologic studies done on fluid from nine patients in this group, and 4 of these were negative (Class I to III); 4 were fairly conclusive (Class IV), and 1 was positive (Class V).

Details on each patient are given in Table 2. In two cases (Cases 1 and 2) the cell block and cytology examinations were negative, while the findings on biopsy were diagnostic. The first of these (Case 1) was thought to have congestive heart failure, and the biopsy and fluid studies were done because the pleural effusion did not clear in response to therapy. The second case (Case 2) had four negative cell blocks before she was referred to our hospital and one negative cell block and cytologic examination after admission. In one additional case with positive findings on biopsy (Case 3), a negative cytologic examination was found and the cell block was not performed.

Two patients (Cases 4 and 5) did not have pleural fluid, and the diagnosis of neoplasia was made only on the basis of the pleural biopsy. It was felt that both were poor risks for thoracotomy, and in one a scalene fat-pad biopsy was negative. As a result of the positive diagnosis thus obtained, x-ray therapy was begun in each case. In an additional case (Case 6) the biopsy specimen was positive for neoplasia, but no studies were done on the pleural effusion. In three (Cases 7, 8, and 9) of the four remaining cases with diagnostic biopsy specimens, both cell block and cytologic examinations were positive. The last case (Case 10) with a positive biopsy specimen had only a positive cell block examination with negative cytology.

In the four patients (Cases 11, 12, 13, and 14) with neoplasms and negative find-

TABLE 2.—*Details on Seventeen Patients*

Case	Age	Sex	Race	Total Protein, Gm./100 Cc.	Cell Block	Cytology	AFB Culture	Routine Culture	Biopsy Diagnosis	Final Diagnosis
1	73	F	W	0.7	Hemorrhagic	I	Neg.	Neg.	Neoplasm	Neoplasm
2	63	F	W	2.5	Neg.×5	I	----	----	Neoplasm	Neoplasm
3	62	F	W	0.6	----	II–III	Neg.	----	Neoplasm	Neoplasm
4	65	F	I	----	----	----	----	----	Neoplasm	Neoplasm
5	60	M	W	----	----	----	----	----	Neoplasm	Neoplasm
6	51	F	W	----	----	----	----	----	Neoplasm	Neoplasm
7	59	F	W	----	Malig.	IV	----	----	Neoplasm	Neoplasm
8	39	F	W	3.5	Malig.	IV	----	----	Neoplasm	Neoplasm
9	76	F	N	----	Malig.	IV	Neg.	Neg.	Neoplasm	Neoplasm (autopsy)
10	71	M	N	6.8	Malig.×2	I	Neg.	Neg.	Neoplasm	Neoplasm
11	76	F	W	----	----	III–IV IV	Neg.	Neg.	Insufficient	Neoplasm (autopsy)
12	65	F	W	3.8	Inflam. malig.	----	Neg.	Neg.	Insufficient	Neoplasm (autopsy)
13	20	M	W	3.8	Malig.	IV V×3	Neg.	Neg.	Ch. pleuritis insufficient	Neoplasm (surgery)
14	66	M	W	2.7	Neg.	----	Neg.	Neg.	Insufficient	Neoplasm (surgery)
15	17	F	W	3.66	Inflam.×5	I III II–III II–III	Neg.×4	Neg.×4	Insufficient	Collagen disease
16	78	F	W	2.8	Inflam.	II–III	Neg.	Neg.	Insufficient	Idiopathic pleural effusion
17	60	F	N	5.4	----	I–III	Neg.	Neg.	Ch. pleuritis	Idiopathic pleural effusion

ings on biopsy, three had either a positive cytology or cell block, while in the last case all studies performed were negative. The diagnosis in these four patients was finally confirmed at autopsy in two and at the time of thoracotomy in the others.

The three patients (Cases 15, 16, and 17) without neoplasia had biopsy diagnosis of insufficient tissue in two cases and chronic pleuritis in one. Cytology, paraffin cell-block studies, and cultures for bacteria fungus and tuberculosis were negative in all three. Skin tests for tuberculosis were negative in two. All three have been followed up to one to one and one-half years with resolution of the effusion, and a diagnosis is still not established. None of these cases have as yet been given chemotherapy for tuberculosis.

Comment

Pleural effusions can be secondary to localized extrathoracic or to systemic causes such as renal disease, cirrhosis, disseminated lupus erythematosus, subdiaphragmatic abscesses, and pancreatitis. Intrathoracic causes may be infectious, neoplastic, traumatic, or due to congestive heart failure. In general, studies in these cases have been limited to radiographic findings and examinations of the fluid obtained by thoracentesis. Total-protein determinations, cell counts, specific gravity, and special chemical studies on the pleural fluid have been helpful, but they do not give an exact etiologic diagnosis. After extrathoracic causes have been eliminated, these laboratory results when coupled with the rest of the clinical findings are of help to the physician. However, cytologic examinations for malignant cells and bacteriologic determinations are more conclusive.

Either because of the type of admissions to our hospital or because of the advanced age of the patients in this series we had no cases of pleural effusion proven to be secondary to tuberculosis. Pleural biopsies in cases of effusion secondary to tuberculosis have been especially rewarding because the condition can be diagnosed and therapy instituted before cultures can be obtained.[1]

The results obtained from studies of malignant cells varies directly with the method used and the experience of the examiner. Robertson,[5] with use of the paraffin cell-block method was able to diagnose 24% of the malignant pleural effusions with certainty. In a study by Graham et al.,[6] with use of the smear technique of McDonald and Broders,[7] carcinoma cells were found in 112 of 221 neoplastic pleural effusions. It is of interest that positive cells were found in the fluid obtained from 88 patients on the first examination and from 24 on the second examination. Myerson [8] found positive cells in 9 of 22 cases with bronchogenic carcinoma and in 2 of 14 cases with metastatic neoplastic effusion. The findings in this series are in agreement with these studies.

The actual microscopic examination of the involved pleura will often yield a more definite diagnosis. Lloyd [9] did biopsies on 23 unselected consecutive cases, with use of a thoracoscope. The biopsy specimens in 12 of the 16 cases with malignancy were diagnostic. Sutliff, Hughes, and Rice [10] removed a rib and performed thoracotomies on 21 patients and demonstrated tuberculosis in 17, carcinoma in 3, and blastomycosis in 1. They did not mention whether or not this is the total number of patients operated on. Small and Landman [11] did a more extensive procedure and actually palpated the lung. They were able to prove tuberculosis in five cases where other methods had been negative. Stead et al.[12] found that only 15 of 24 cases suspected of having tuberculous pleural effusion had tuberculosis when the patients were subjected to open pleural biopsy. Sixteen consecutive cases were studied by Breckler, Hoffman, Hill, Hensler, and Hukill.[13] The first five cases had both Vim-Silverman needle biopsy and open pleural biopsy. Subsequently, only the open biopsy was done on the remaining patients, because the authors felt it yielded better results. These two meth-

ods were not compared in their study, however. In their total cases, four were proven to have tuberculosis by histologic examination and five only by detection of acid-fast bacilli by stain or culture of the material obtained by biopsy. The biopsy was noncontributory in one additional case of tuberculosis which was subsequently proven by a positive sputum examination. Two cases of intrathoracic neoplasm were diagnosed by biopsy, while the biopsy was noncontributory in their remaining cases.

In the first report on needle biopsies of the pleura by DeFrancis, Klosk, and Albano,[1] tuberculous pleuritis was diagnosed in two cases. Subsequently, a larger series of 20 patients was reported by Heller, Kellow, and Chomet.[2] There were five biopsy diagnoses of tuberculosis, four of neoplasm, and nine of nonspecific fibrosis, and two specimens which were insufficient for diagnosis. Two of the cases of nonspecific fibrosis were subsequently shown to have neoplasia, but in one the pleura was not involved. This method has also been used by Katz, Donohoe, and Mathews with good results, but the exact details are not known.[3]

Heller et al.[2] reported only one small hemothorax in 22 biopsy specimens. In this series two cases had minor complications of transient evidence of blood in the postbiopsy pleural fluid. I do not feel that complications are any greater than with routine thoracentesis if suitable precautions are used.

Conclusion and Summary

With the introduction of needle biopsy of the parietal pleura by DeFrancis, Klosk, and Albano,[1] an easy method of biopsy was made available which could even be carried out in outpatients. The results of 17 biopsies of the parietal pleura are presented and compared with other studies. There were 10 positive biopsy specimens in 14 cases of neoplasm and 3 noncontributory biopsy specimens in patients in whom a diagnosis has still not been established after one to one and one-half years. The method is useful but not fool-proof, and a negative biopsy specimen does not rule out tuberculosis or neoplasia. In a few cases the final answer will only come from thoracotomy, long follow-up, or autopsy.

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Comparative Clinical and Biochemical Effects of the Dextro- and Levo- Isomers of Thyroxine

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The clinical and physiological comparisons of the isomers of thyroxine by a number of investigators are well summarized by Tabachnik et al. in a recent publication.[1] Some excellent animal measurements of oxygen consumption suggest complete lack of potency of the dextro- isomer,[2] whereas other studies,[3] with use of a different phenomenon, demonstrate physiological activity. Most of these studies were done with racemic mixtures of the two isomers, as compared with the results of the administration of the levo- isomer alone. A generous provision of unlimited quantities of sodium D-thyroxine, suitable for clinical studies, has permitted an extended series of human observations.* Amounts of the sodium D-thyroxine sufficient to administer 100 times the usual levo- isomer dosage have made possible hitherto unavailable comparisons. The present studies, however, were done at the dose levels regularly used clinically in the treatment of hypothyroidism with L-thyroxine.

The chemical characteristics of the two isomers are given below.[4]

Submitted for publication July 15, 1957.

Supported by Baxter Laboratories, Inc., Morton Grove, Ill.

From the School of Medicine, Department of Medicine, the University of Southern California, and the Thyroid Clinic, Los Angeles County Hospital.

* Sodium levo-thyroxine (Synthroid) and sodium dextro-thyroxine were supplied by Dr. Robert Herwick and Dr. Leonard Ginger, of the Baxter Laboratories, Inc., Morton Grove, Ill.

The purity of the isomers is indicated by the rotation observations. But a much more striking indication of the complete lack of contamination of the dextro material by any L-thyroxine is shown in Figures 3 and 4; 10 mg. of the dextro- material fails to produce the electrocardiographic change produced by 25μg. of the levo- preparation.

Methods of Study

Hypothyroid patients were selected from the Thyroid Clinic of the University of Southern California and the Los Angeles County General Hospital. The etiology in these cases was (1) athyreotic, spontaneous idiopathic or therapeutic; (2) hypofunctional, thyreotic or pituitary. These patients were studied by clinical observation, serum protein-bound iodine (method of Barker), radioactive-iodine uptake, serum cholesterol, electrocardiogram, serum albumin-globulin ratio, and basal metabolic rate. These patients were usually ambulatory, occasionally hospitalized.

Sodium L-thyroxine was administered in various dose levels for several weeks. This was followed by sodium D-thyroxine given in various amounts by oral daily dosage.

Groups of normal medical students with radioactive-iodine uptake measurements of about 20% in 24 hours were given a placebo, a capsule of potassium iodide, sodium L-thyroxine, or sodium D-thyroxine, once daily by mouth for eight days. Twenty-four-hour radioactive-iodine uptake was measured before these medications were initiated and on the seventh and eighth days during the administration of these medications. The comparison of the effect on depression of the radioactive iodine uptake is tabulated below (Table 7). The brief history of an athyreotic patient is given below with accompanying chart (Fig. 1) of ob-

Chemical Characteristic

	Sodium L-Thyroxine	Sodium D-Thyroxine
Amount	250 mg.	250 mg.
Moisture, %	8.58	5.93
I (anhydrous), %	62.2	62.5
N (anhydrous), %	1.66	1.72
$[\alpha]^t_D$	−5.3 (t=22 degrees)	+5.6 (t=25 degrees)

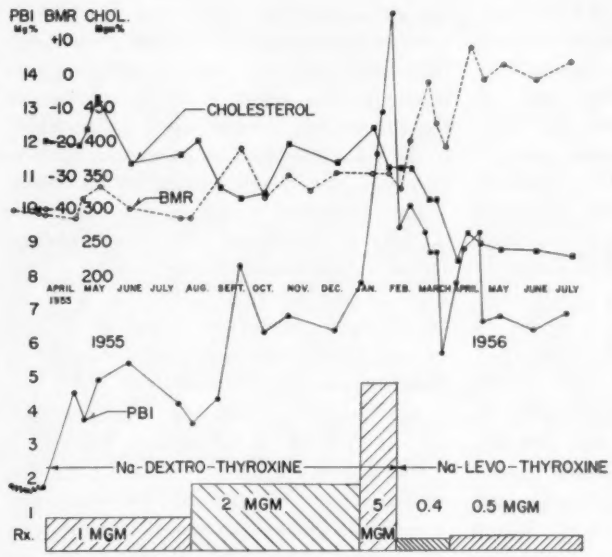


Fig. 1 (Case 14).—Thyrotropic hormone response test was done before initiation of treatment, with radioactive-iodine uptake preceding TSH, 7.5%, uptake after three days of 10 U. S. P. units of intramuscular TSH daily, 5.7%. This indicated the absence of functioning thyroid tissue. Note that the serum protein-bound iodine level alternately produced by 0.5 mg. of sodium L-thyroxine is approximately the same as that produced by 2.0 mg. of D-thyroxine. The basal metabolic rate, however, was about —30% with D-thyroxine and 0% with L-thyroxine. The serum cholesterol was about 350 mg. per 100 cc. with D-thyroxine and about 250 mg. with L-thyroxine. The increase of the dose of D-thyroxine to 5 mg. daily apparently makes a slight decrease in the serum cholesterol but does not significantly change the basal metabolic rate.

servations during medication with D- and L-thyroxine.

CASE 14.—A 49-year-old Negro woman was discovered to have hyperthyroidism in December, 1953, when her serum protein-bound iodine was 13.7μg. and 11.8μg. per 100 cc.; radioactive iodine uptake was 92%; a dose of 7 mc. of radioactive iodine was given on Dec. 14. The first post-therapy serum protein-bound iodine test was 2.3μg. per 100 cc. on Feb. 24, indicating an extremely rapid total thyroidectomy resulting from radioactive-iodine therapy. Subsequent values were as low as 1.1μg. per 100 cc. Treatment with desiccated thyroid was started at a dose level of ¼ grain (16.2 mg.). There were no medical complications. After an interval without therapy, the protein-bound iodine again was found to be 1.0μg. per 100 cc., as shown in Figure 1.

Results

The calorigenic effect of sodium L-thyroxine well correlated in our experience with the level of the serum protein-bound iodine.[5] It was of interest to establish the level of serum protein-bound iodine produced by the administration of sodium D-thyroxine. The results of these studies are shown in

TABLE 1.—*Demonstration of Serum PBI Produced by the Same Oral Dosage of Sodium* D-*Thyroxine and Sodium* L-*Thyroxine*

Case	Medication, Mg.	Average PBI	Average Chol.	BMR	Isomer Dosage, Days
	A. Hypothyroidism with No Functioning Thyroid Tissue				
1 *	Na-D-Th 0.3	2.7	487	—22	101
	Na-L-Th 0.3	6.4	308	—12	330
2 †	Na-D-Th 0.1	1.8	426	— 7	35
	Na-L-Th 0.1	3.6		+19	29
	Na-D-Th 0.2	2.1	475	—18	14
	Na-L-Th 0.2	6.9	298	+18	27
	B. Hypothyroidism with Functioning Thyroid Tissue				
3 ‡	Na-D-Th 0.3	4.9		—10	74
	Na-L-Th 0.3	7.2	252	+10	44
4 §	Na-D-Th 0.8	5.4		—11	26
	Na-L-Th 0.8	7.7		+10	82

* PBI 1.0, uptake 5.3%, uptake after TSH —7.3%.
† PBI 0.8, uptake 1.7%, uptake after TSH —0.31%. Indicating no thyroid responsiveness. Tests were done before treatment.
‡ PBI before treatment 3.1, I^{131} uptake 1%, I^{131} uptake after TSH 29%, indicating thyroid responsiveness. Tests were done before treatment.
§ PBI before treatment 2.8, I^{131} uptake before TSH 23.6%, I^{131} uptake after TSH 56%.

four patients in Table 1. Table 1*A* indicates the level of serum protein-bound iodine produced in patients having no functioning thyroid tissue as established by lack of radioactive-iodine-uptake response to TSH. In these two patients, the serum protein-bound iodine level produced by a dose of D-thyroxine was about half that produced by the same dose of sodium L-thyroxine. The length of time on the dextro- isomer is shown extending from 2 weeks to 101 days. Whether or not this difference is due to malabsorption in the gastrointestinal tract or excessive excretion by the liver of the dextro- isomer is at present not established.

In Table 1*B*, the two patients, although having hypothyroidism as indicated by subnormal serum protein-bound iodine values, were found to have functioning thyroid tissue as indicated by significant response to thyrotropic hormone. In these two patients, the level of serum protein-bound iodine produced by D-thyroxine is approximately two-thirds or more of that produced by the same dose of sodium L-thyroxine. The duration of administration of dextro-isomer thyroxine was 26 to 74 days. The greater level of serum protein-bound iodine produced by D-thyroxine in these patients with functioning thyroid tissue may be due to the fact that this level is composed of exogenous thyroid as well as the endogenous serum thyroxine; a later study (Table 7), has shown that the D-thyroxine is relatively weak in suppression of I^{131}, and, hence, the reduction in pituitary function in these cases is slight. The result is the summation of the endogenous protein-bound iodine added to the value produced by exogenous medication. If the serum protein-bound iodine before treatment (Case 3, 3.1, and Case 4, 2.8) is subtracted from protein-bound iodine values found during therapy ($4.9-3.1=1.8$ and $5.4-2.8=2.7$), the values attributable to exogenous medication then become much more nearly of the order of that found in athyreotic patients (Table 1*A*).

In comparison with the results demonstrated in Table 1, the patients reported in Table 2 were treated by increasing the dose of sodium D-thyroxine until the serum protein-bound iodine approached that produced by sodium L-thyroxine. It was found that five times the oral dose of D-thyroxine as compared to L-thyroxine was needed to produce the same protein-bound iodine. This would appear to be true even when the dose of sodium L-thyroxine was as low as 0.1 mg. a day or as high as 0.4 mg. a day. The mechanism responsible for this fivefold difference in dosage has not been elucidated.

Relatively massive doses of sodium D-thyroxine produced serum protein-bound iodine levels usually regarded as associated with hyperthyroidism (Table 3). In these patients, even when the maximum dose of

TABLE 2.—*Demonstration of Dosage of Sodium* D-*Thyroxine Required to Produce the Same PBI Level as Produced by Sodium* L-*Thyroxine*

Case	Medication, Mg.	Average		BMR	Isomer Dosage, Days
		PBI	Chol.		
5	Na-D-Th 1.0	5.2	333	−8	161
	Na-L-Th 0.2	5.9	295		69
6	Na-D-Th 2.0	6.4	447	−6	119
	Na-L-Th 0.4	6.6	340	+13	189
7	Na-D-Th 0.5	4.5	277	−17	340
	Na-L-Th 0.1	4.8	275	−12	119
8	Na-D-Th 1.5	7.1	319	−23	112
	Na-L-Th 0.3	6.9	225	−5	357
2	Na-D-Th 0.5	3.7	464	−21	32
	Na-L-Th 0.1	3.6		+19	152
9	Na-D-Th 1.0	6.2	341	−31	200
	Na-L-Th 0.2	5.8	294	−21	210
10	Na-D-Th 1.5	6.8	220	−12	160
	Na-L-Th 0.3	6.8	219	−3	231

TABLE 3.—*Massive Sodium* D-*Thyroxine Dosage Effects* *

Case	Medication, Mg.	PBI	Chol	BMR	Given D Since L, Days	Time Given D at Max. Dose, Days
11	Na-D-Th 3.0	11.6	206	−22	76	53
	Na-D-Th 4.0	16.7	211	−18	144	68
12	Na-D-Th 5.0	16.4	320	− 7		26

* 3.0 mg. and over.

D-thyroxine had been administered 34 to 68 days, the basal metabolic rate was still subnormal. In one case (Case 14), serum cholesterol was abnormally elevated and the basal metabolic rate remained at −27% even when the serum protein-bound iodine was 16.4μg. per 100 cc.

The possibility that D-thyroxine would correct elevated serum cholesterol levels was one of the reasons for initiating these studies. If the serum cholesterol could be corrected without thyrotoxicity, this material would be considered clinically useful in hypercholesterolemia. This, unfortunately, does not seem to be the case with the dosage used in this study as shown in Table 4. In Table 4*A*, patients who have been maintained for several months with sodium L-thyroxine with established serum protein-bound iodine levels and serum cholesterol values were then changed to oral maintenance dosage of five times the dosage of sodium L-thyroxine. This maintained the level of serum protein-bound iodine, but the serum cholesterol in all cases except one rose to what are considered pathologic levels. The reverse procedures were carried out with patients who had been maintained with large dosage of D-thyroxine and who were then changed to oral sodium L-thyroxine (Table 4*B*). In each case, there was a decrease of serum cholesterol upon the administration of L-thyroxine as compared with the previous D-thyroxine. This is noted in Case 14, who, being maintained with 5 mg. of sodium D-thyroxine, has established a serum protein-bound iodine of 16μg. per 100 cc. with an accompanied serum cholesterol of 320 mg. Upon being changed to 0.4 mg. of sodium L-thyroxine, with a serum protein-bound iodine of 5.9, serum cholesterol dropped to 225 mg.

The intravenous injection of D-thyroxine was demonstrated by Pitt-Rivers and Lerman [6] to have approximately one-tenth the calorigenic effectiveness of L-thyroxine. The fivefold dosage of sodium D-thyroxine as compared to L-thyroxine was unable to sustain the basal metabolic rate in ambulatory patients.

The average ambulatory basal metabolic rate measurement with sodium L-thyroxine is shown in Table 5*A*. In each instance, when the patient was changed to the fivefold dose of sodium D-thyroxine, a gross decrease in the basal metabolic rate test resulted,

TABLE 4.—*Effect of Sodium* D-*Thyroxine on Serum Cholesterol*

Case	1st Medication, Mg.	Prechange		2d Medication, Mg.	Days After Change	Chol.	PBI	Chol. Mg.
		Chol.	PBI					
	A. Maintained with Na-L-Th (1st medication), Changed to Na-D-Th (2d medication)							
5	0.3	285	7.5	1.0	44	375	6.5	+ 90
6	0.4	330	7.2	2.0	49	470	6.1	+140
13	0.2	295	7.7	0.75	77	330	7.4	+ 35
8	0.3	220	5.7	1.5	56	355	6.6	+135
9	0.2	195	5.9	1.0	33	295	6.1	+100
10	0.3	230	6.8	1.5	42	200	8.5	− 30
	B. Maintained with Na-D-Th (1st medication), Changed to Na-L-Th (2d medication)							
5	1.0	325	4.6	0.2	58	295	6.4	− 30
14	5.0	320	16.4	0.4	42	225	5.9	− 95
3	1.0	345	7.1	0.2	68	220	7.3	−125
7	0.5	285	5.0	0.1	56	210	6.2	− 75
8	1.5	317	7.8	0.3	29	220	11.2	− 97
2	1.0	400	5.2	0.2				

TABLE 5.—*Comparative Effects of Sodium* D-*Thyroxine and Sodium* L-*Thyroxine on BMR*

Case	1st Medication, Mg.	Prechange BMR	Wgt.	Plse.	PBI	2d Medication, Mg.	Days After Change	BMR	Wgt.	P.	PBI
A. Maintained with Na-L-Th (1st medication), Changed to Na-D-Th (2d medication)											
6	0.4	+17	145	73	7.2	2.0	49	−17	161	68	6.1
8	0.3	− 3	217	64	5.7	1.5	56	−22	223	56	6.6
9	0.2	−23	186	76	5.9	1.0	28	−32	182	54	6.1
10	0.3	+ 1	123	80	6.8	1.5	42	−32	128	60	8.5
B. Maintained with Na-D-Th (1st medication), Changed to Na-L-Th (2d medication)											
14	5.0	−28	142	60	16.4	0.4	42	−17	134	68	5.9
3	1.0	− 6	155	72	7.1	0.2	68	+ 3	153	68	7.3
8	1.5	−20	221	56	7.8	0.3	29	+12	217	60	11.2

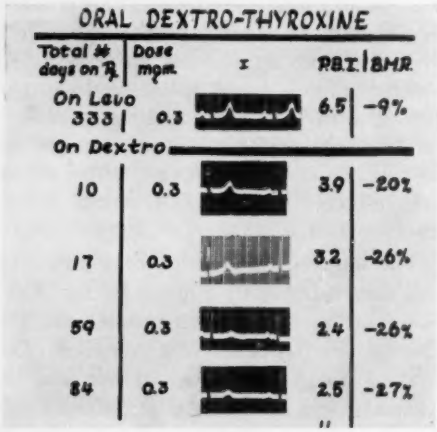
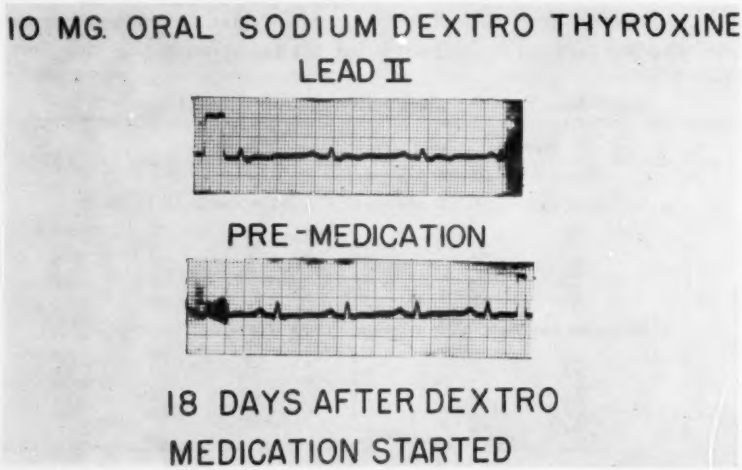


Fig. 2.—Successive Lead I complexes at 10, 17, 59, and 84 days with 0.3 mg. oral daily dose of sodium D-thyroxine.

with an associated decrease in the pulse rates, although the serum protein-bound iodine remained about the same, and, conversely (Table 5*B*), when the patient being maintained with sodium D-thyroxine was changed to sodium L-thyroxine, there was a rise in the basal metabolic rate test and an increase in the pulse rate.

A comparison of the effects of D-thyroxine and L-thyroxine on the electrocardiogram, at the L-thyroxine euthyroid dose level, is shown in Figure 2. The athyreotic myxedematous patient given 0.3 mg. of sodium L-thyroxine shows, if anything, excessive potential in Lead I, whereas the same patient after two months of the same dose of D-thyroxine with resulting reduction of

Fig. 3.—Lead II in a myxedematous patient before and after 18 days of massive, 10 mg. daily oral dosage of sodium D-thyroxine. Note the increased rate and slight increase of potential but no appearance of T waves.



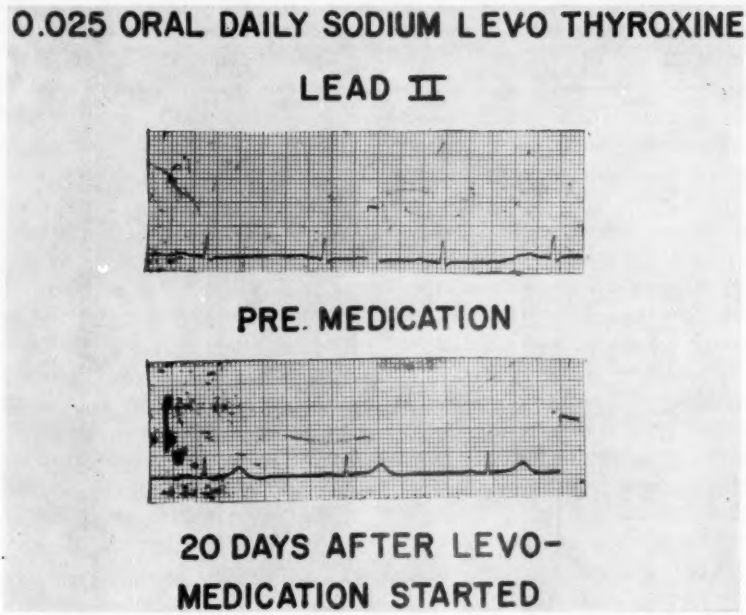


Fig. 4.—Lead II in a myxedematous patient before and after 20 days of small, 0.025 mg., daily oral dosage of sodium L-thyroxine. Note the absence of tachycardia but the pronounced effect on the potential of the T waves.

protein-bound iodine and basal metabolic rate has a much reduced potential in the electrocardiogram. It is evident that the pharmacodynamic action of D-thyroxine is much less than that of L-thyroxine.

The effect of D-thyroxine on the electrocardiogram in one untreated myxedema patient was found to be extremely slight, as demonstrated in Figure 3. A massive oral dose of 10 mg. a day of sodium D-thyroxine in an athyreotic patient raising the serum protein-bound iodine from 1.5μg. per 100 cc. to 14.7μg. per 100 cc. (Table 7) is associated with very slight changes in the electrocardiogram. The basal metabolic rate had risen from -40% to -15%. This is in contrast to the demonstration in Figure 4 of the effect of a small oral dose of sodium L-thyroxine, 0.025 mg. by mouth daily. In the untreated myxedema patient, the pretreatment electrocardiogram is shown to be of low voltage with a flat T wave in all leads, whereas after 20 days of medication with this minute dose of L-thyroxine the potential and the T wave are considerably increased.

The physiological action of D-thyroxine is best demonstrated by its effect in suppressing the uptake of radioactive iodine in normal subjects, as shown in Table 6. When normal subjects are given the placebo for eight days and the radioactive iodine uptake on the seventh and eighth days is compared with that before medication, the second uptake on the placebo is 16% less than the pretreatment uptake. If the subject is given 0.5 mg. of sodium L-thyroxine daily by mouth for eight days, the radioactive-iodine uptake on the seventh and eighth days is depressed by 82% of the pretreatment value. If an amount of potassium iodide containing the same amount of iodine as is found in an equivalent amount of thyroxine is given, the second uptake is depressed exactly the same amount as the placebo, namely, 16.8%, and if D-thyroxine dosage of 0.5 mg. orally is given, the second test is depressed 40%, as much as the first test. This is evidently a significant depression only half as great as

TABLE 6.—*Comparative I^{131} Suppression Tests in Normal Subjects Given Placebo, Potassium Iodide, Sodium L-Thyroxine and Sodium D-Thyroxine*

Case	Before Medication			After Medication			Average Diff. 1st-2d I^{131} Uptake, %
	I^{131} Uptake	PBI	Chol.	I^{131} Uptake	PBI	Chol.	
			Placebo				—17
15	26.7%	4.3 (6)	235	23.0%	6.6 (5)	280	
16	25.6	6.0 (6)	230	20.1	6.1 (6)	215	
17	20.0	5.6 (11)	280	15.3	7.8 (8)	290	
18	20.5	6.3 (6)	360	19.3	6.4 (5)	345	
19	16.8	5.9 (11)	270	13.6	6.2 (10)	395	
20	17.9	4.3 (3)	320	15.3	4.7 (4)	325	
			Sodium L-Thyroxine *				—82.0
21	39.5	5.5 (9)	295	4.1	11.7 (9)	285	
22	28.0	6.4 (10)	300	2.2	8.8 (7)	300	
23	21.4	16.9 (5)	275	3.1	8.0 (1)	275	
24	29.3	6.4 (5)	280	6.3	9.0 (3)	245	
25	19.0	6.1 (8.5)	--	5.3	9.2 (3)	290	
26	15.4	6.2 (6)	240	2.5	8.3 (3)	195	
27	31.5	8.1 (5)	230	8.7	10.2 (2)	260	
			Potassium Iodide †				—18.2
21	18.4	4.5 (2)	220	17.8	3.7 (1)	185	
24	20.4	5.1 (3)	275	13.9	5.3 (7)	255	
28	20.2	3.4 (6)	275	16.9	3.4 (5)	245	
29	28.1	3.8 (11)	225	25.3	4.5 (13)	270	
30	21.6	4.3 (1)	255	25.6	4.5 (1)	245	
31	23.0	4.0 (2)	265	16.1	4.1 (3)	270	
32	12.2	3.9 (3)	245	11.8	3.5 (4)	225	
33	29.4	4.3 (3)	270	20.7	3.1 (3)	250	
34	19.5	4.3 (3)	310	15.6	4.0 (2)	315	
35	24.2	5.2 (1)	160	15.1	4.4 (2)	155	
36	24.8	3.9 (4)	305	15.6	4.1 (7)	325	
			Sodium D-Thyroxine ‡				—39.7
37	27.5	7.4 (2)	175	8.0	7.0 (1)	215	
38	26.0	8.7 (2)	285	10.0	5.0 (2)	355	
39	27.0	8.7 (4)	220	13.0	6.4 (2)	275	
18	18.5	8.4 (4)	160	9.0	4.8 (3)	220	
40	18.0	6.8 (2)	260	10.0	5.8	345	
21	24.5	5.5 (4)	155	16.0	6.8 (2)	235	
14	28.7	9.2 (5.5)	320	27.2	6.2 (1)	290	
41	11.9	5.2 (6)	220	8.5	5.7 (3)	200	
42	20.0	7.3 (7)	335	12.1	6.8 (1)	290	
43	23.4	5.4 (8)	240	15.1	5.6 (3)	195	
44	32.9	6.5 (4)	275	21.6	8.2 (1)	265	
45	17.4	5.1 (7)	190	15.9	7.3 (0)	190	

* 0.5 mg. sodium L-thyroxine (oral).
† 0.320 μg. iodide to 0.5 mg. thyroxine.
‡ 0.5 mg. sodium D-thyroxine.

that produced by L-thyroxine but is more than twice as great as the depression produced by the placebo or potassium iodide. This is a definite indication of physiological action. Statistical analysis indicates that the difference between the standard error of the means of the placebo and either the L-thyroxine or the D-thyroxine has a *P*-value of less than 0.001 in each case. The similar difference between the L-thyroxine effect and and D-thyroxine effect also has a *P*-value of less than 0.001.

It is interesting to note that there is no significant change in serum cholesterol associated with either the placebo, potassium iodide, or L-thyroxine but that in half of

TABLE 7 (Case 46).—*Laboratory Data on a Myxedema Patient Given 10 Mg. of Sodium D-Thyroxine Daily*

Date	PBI, μg./100 cc.	Inorg. I, μg./100 cc.	Chol., Mg./100 cc.	BMR, %	Weight, Lb.	Pulse	ECG	Time, Days Treatment	Treatment
				Below					
7/11/56	1.2	3	600	—40	185 ¾	58	X		None
7/12/56	1.5	5	600						None
7/13/56				—35	185 ½	66			Na-D-Th, 10.0 mg.
7/16/56	11.4	4	585					4	Na-D-Th, 10.0 mg.
7/17/56	11.4	8	525	—27	183	74	X		Na-D-Th, 10.0 mg.
7/20/56			405	— 9	181 ¾	82	X	7	Na-D-Th, 10.0 mg.
7/23/56	17.2	7	410	—21	179	78	X	9	Na-D-Th, 10.0 mg.
7/24/56	13.9	5	330					13	Na-D-Th, 10.0 mg.
7/26/56				—21	177	72	X		Na-D-Th, 10.0 mg.
7/31/56	14.7	12	282	—15	174	76	X	18	Na-D-Th, 10.0 mg.

the subjects treated with D-thyroxine there was apparently a rise of serum cholesterol. In the remainder of the cases, however, there was no significant change. In those cases in which the significant rise in serum cholesterol occurred there was a greater depression of uptake.

The experience in a single case, with the largest dose of D-thyroxine used, 10 mg. a day, is shown in Table 7. This would indicate that in this case, at this dose level, the isomer is calorigenic and that it has a significant effect on serum cholesterol. It must be admitted, however, at this dose level a contamination as little as 1% with the L-thyroxine isomer would constitute an effective dose of that isomer. Thus, at 10 mg. a day of D-thyroxine, 1% contamination with L-thyroxine would constitute 0.1 mg., which is an effective dose.

The electrocardiogram shown in Figure 3, however, was done on this patient (Case 46) and shows so little electrocardiographic change that the absence of any effective amount of L-thyroxine is indicated. We have concluded that this experiment warrants more extended studies of what seems to be an effect of excessive doses of D-thyroxine.

The lower dosage of D-thyroxine has been shown to be effective in depressing pituitary function (I^{131} uptake, Table 6) but not to be calorigenic; this would seem to explain the rise of serum cholesterol with the smaller dose, whereas the excessive dose shown in Table 7 was able to raise the BMR and depress the serum cholesterol. Hence, it may be concluded that small doses of D-thyroxine raise serum cholesterol, while large doses depress it.

Comment

The effects on serum protein-bound iodine are doubtless related to the factors of globulin binding in the serum.[7] This may well be the result of the large volume of distribution of the thyroxine, demonstrated by radioactive iodine studies of Robbins, Rall, Becker, and Rawson,[7] and indicated by serum half-life of D-thyroxine as compared to L-thyroxine which they found. The established effects of D-thyroxine on radioactive iodine uptake in normal subjects previously reported[10] and reconfirmed in this study corroborate the histologic effects in the pituitary found by Griesbach, Kennedy and Purves.[3]

It has been suggested that the cholesterolytic effect of the massive oral dose of D-thyroxine may be the result of the production of significant amounts of deaminated analogues. These substances have a calorigenic action probably less than 30% as great as L-thyroxine. Since the analogues have no asymmetric carbon atom and hence no optical activity, origination from either isomer does not affect potency. The cholesterolytic effect of any dose of D-thyroxine, then, might depend on the rate of its deamination. The important actions of deaminated triiodothyronine have recently been reported.[11]

Conclusion

In the athyreotic myxedematous patients, an oral dosage of sodium D-thyroxine, similar in amount to that of L-thyroxine used in the treatment of hypothyroidism, produced about one-third the serum protein-bound iodine level as an equal dose of sodium L-thyroxine.

It requires five times the oral dosage of sodium D-thyroxine to produce the level of serum protein-bound iodine produced by sodium L-thyroxine. In the noncalorigenic dose level, the sodium D-thyroxine had an insignificant effect on the serum cholesterol. Even a massive oral daily calorigenic dosage of 10 mg. in one patient had a very slight effect on the potential of the electrocardiogram. A noncalorigenic oral daily dosage of 0.5 mg. of sodium D-thyroxine, however, is again shown to depress the radioactive iodine uptake by 40% at the end of seven days. In a single case, a massive dosage of sodium D-thyroxine was found to increase the basal metabolic rate and lower serum cholesterol without affecting the electrocardiogram.

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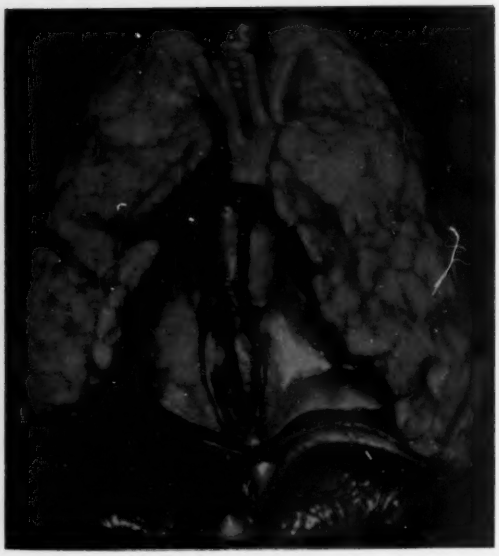
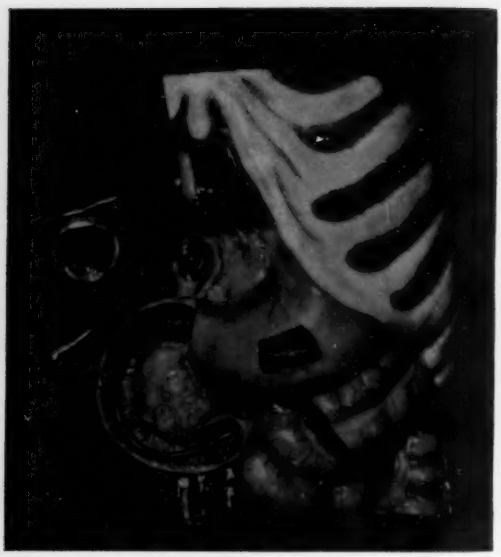


Esophageal lavage

Gastric lavage



Duodenal drainage

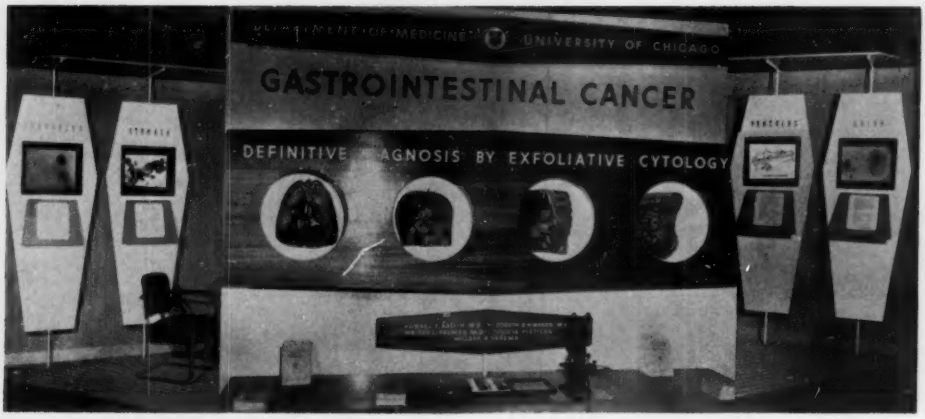
Colonic irrigation

Esophageal Lavage.—This manikin illustrates a No. 18 Levin tube situated just distal to an infiltrative squamous-cell carcinoma preparatory to irrigation.

Stomach Lavage.—A No. 18 Levin tube in position near an ulcer of undetermined etiology of the lesser curvature of the stomach.

Duodenal Drainage.—By means of a double-lumen Diamond tube exfoliated malignant cells may be recovered from carcinomas of the pancreas, common bile duct or gallbladder.

Colonic Irrigation.—Malignant cells can be recovered from carcinomas of the cecum and splenic flexure by irrigation through a No. 12 Ewald tube inserted to the rectosigmoid.



Illustrated Article

Gastrointestinal Cancer

Definitive Diagnosis by Exfoliative Cytology

HOWARD F. RASKIN, M.D.; JOSEPH B. KIRSNER, M.D.; WALTER L. PALMER, M.D.; SYLVIA PLETICKA, B.S., and WILLARD A. YAREMA, A.B., Chicago

Introduction

In recent years exfoliative cytology has become increasingly useful as a method of diagnosing cancer of the gastrointestinal tract. The cytologic procedures, as illustrated on the following pages, demonstrate the relative simplicity of the techniques. The methods of obtaining malignant cells from the esophagus, stomach, duodenum, and colon are satisfactorily performed by trained cytotechnicians. The presence of a physician is required for the occasional difficult intubation and for final interpretation of slides. It is most advisable for the person who actually performs the test to read the slides in order to evaluate the material best. Certain fundamentals of technique should be adhered to strictly. For instance, the least possible delay between aspiration and fixation of the material is constantly stressed in order to achieve good cellular preservation. A measure of skill is required in manipulating esophageal and gastric tubes when obstruction, gastroenterostomy, subtotal resection, or other anatomical abnormalities are encountered; the quality and quantity of the cellular yield are dependent upon the thoroughness of the lavage.

From the Department of Medicine, University of Chicago, The School of Medicine.

Shown as a scientific exhibit of the Section on Gastroenterology and Proctology at the 106th Annual Meeting of the American Medical Association, New York, June 3-7, 1957.

This project was supported by a field investigation grant from the National Cancer Institute, National Institutes of Health, U. S. Public Service, and by the Stewart Fund to the University of Chicago.

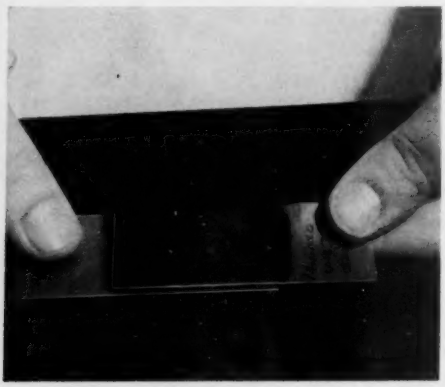
Esophageal Lavage

1. Patient is fasted overnight. A #18 F. rubber Levin tube is passed through the mouth to the 45 cm. mark.

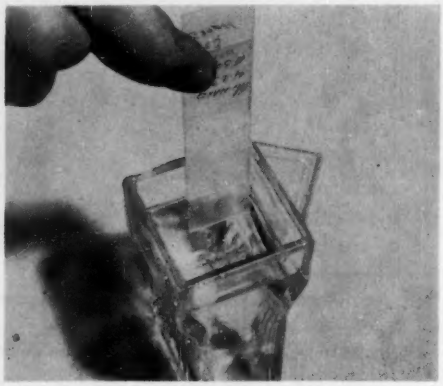
2. An attempt is always made to pass the tube beyond an esophageal obstruction and enter the cardia. One hundred cubic centimeters of isotonic saline solution is swallowed and gently aspirated at the cardia.

3. The tube is then withdrawn in 5 cm. segments. At each level a 20-40 cc. saline lavage is performed.

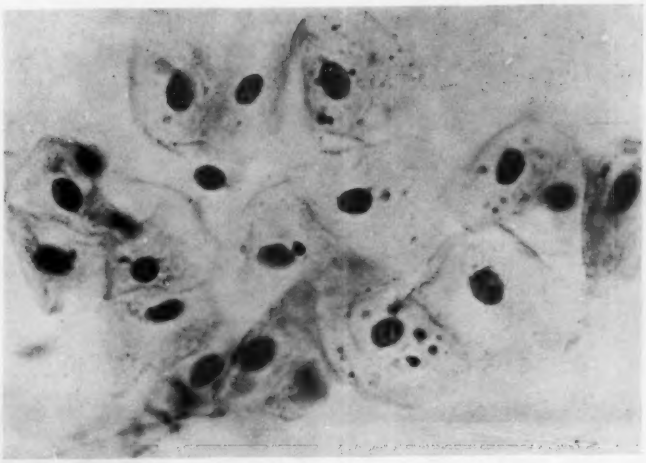
4. The aspirate is centrifuged at 5000 rpm for two minutes.



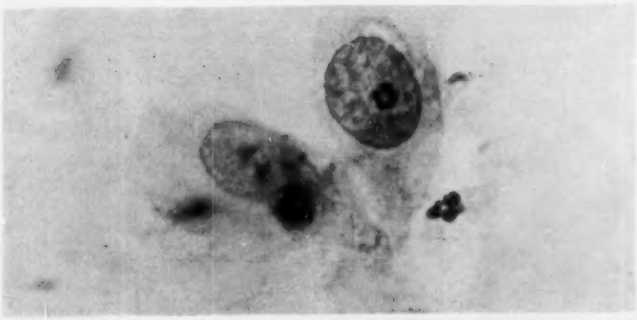
5. Cellular material is smeared on frosted slides.



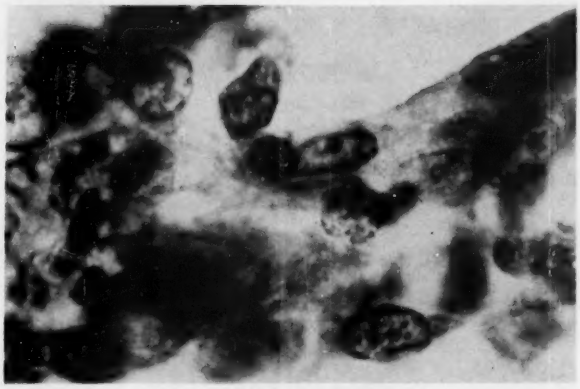
6. The two slides are placed back to back in an ether-alcohol mixture and then stained by the Papanicolaou method.



7. Normal esophageal squamous cells: oval, centrally located nuclei with a normal nuclear-cytoplasmic ratio.



8. Well-differentiated squamous-cell carcinoma, revealing enlarged nuclei, prominent nucleoli, and chromatin clumping.



9. Undifferentiated squamous-cell carcinoma with heavy chromatin clumping and irregular nuclear borders.

ESOPHAGEAL CYTOLOGY RESULTS

TOTAL CASES - 121

CLINICALLY BENIGN	68	CLINICALLY MALIGNANT	53
CYTOLOGY NEGATIVE	67	CYTOLOGY POSITIVE	50
CYTOLOGY FALSE POSITIVE	1	CYTOLOGY FALSE NEGATIVE	3

10. A cytologic false-positive report denotes a misinterpretation of benign cells as malignant. A cytologic false-negative result indicates a failure to find or to recognize tumor cells when malignancy is present.

Gastric Lavage

1. After an overnight fast a #18 F. Levin tube is passed orally to the antrum and the gastric residuum is aspirated. The stomach is then barbotaged vigorously for three minutes, using 300 cc. of saline solution, which is saved for cytologic studies.

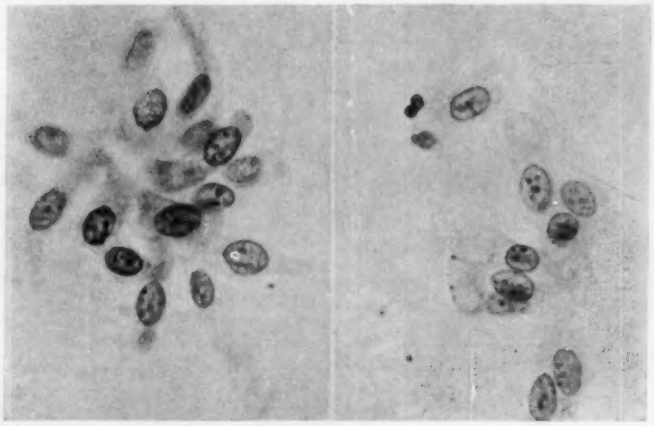
2. Five hundred cubic centimeters of sodium acetate buffer solution is then instilled.

3. The patient is placed on his right side: The position is rotated 90 degrees every two minutes.

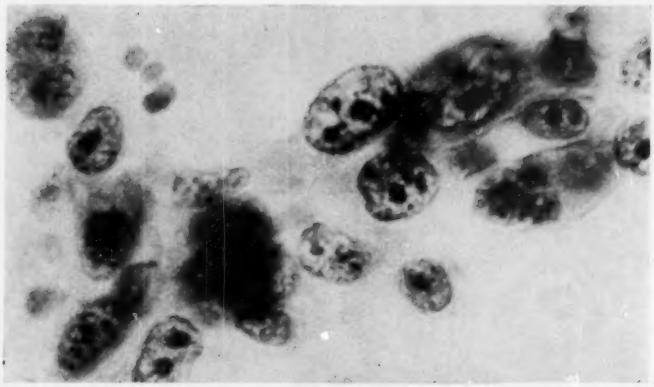
4. The patient is prone for two minutes.

5. The patient is on his back two minutes; stomach massaged.

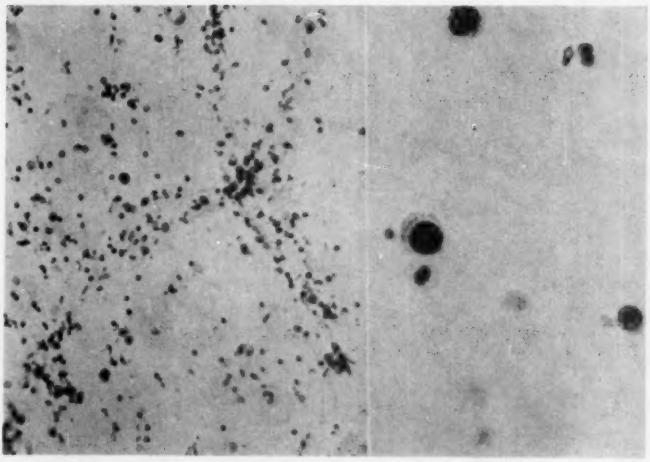
6. With the patient in the left lateral decubitus, the fluid is removed.



7. Normal gastric columnar epithelial cells originating from the gastric fundus (left) and the gastric antrum (right).



8. Malignant cells from an infiltrating carcinoma of the lesser curvature. Dense nuclear chromatin clumping is the outstanding feature of these cells.



9. Two gastric lymphoma cells (lymphoblasts), as seen under low-power magnification (× 100 left) and higher power (× 450 right).

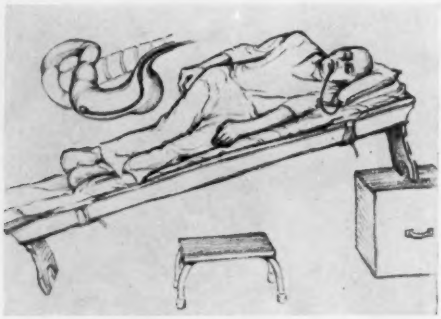
GASTRIC CYTOLOGY RESULTS

TOTAL CASES - 501

CLINICALLY MALIGNANT	98	CLINICALLY BENIGN	403
CYTOLOGY POSITIVE	93	CYTOLOGY NEGATIVE	400
CYTOLOGY FALSE NEGATIVE	5	CYTOLOGY FALSE POSITIVE	3

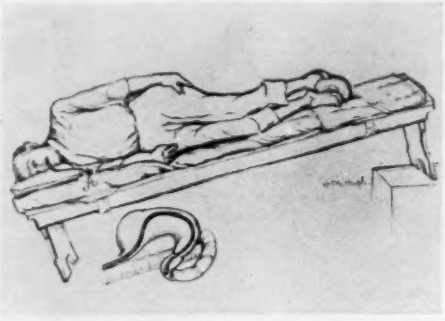
Duodenal Drainage

1. Method of rapid intubation: A double-lumen gastroduodenal tube (Diamond tube) is passed to the 45 cm. mark.

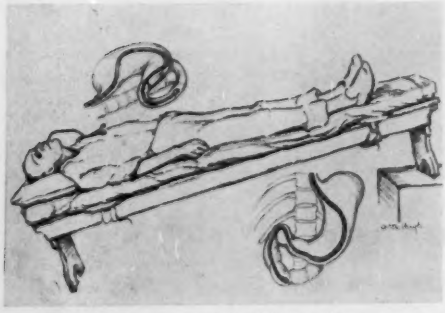


2. With the patient lying on the left side on an elevated cot, the tube is swallowed an additional 15 cm. so as to lie along the greater curvature.

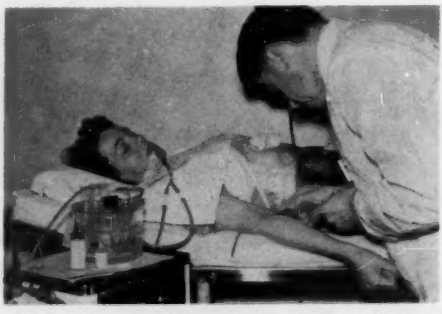
3. The patient bends forward and takes several deep breaths; the tip of the tube slips into the antrum as the anterior wall of the stomach falls forward.



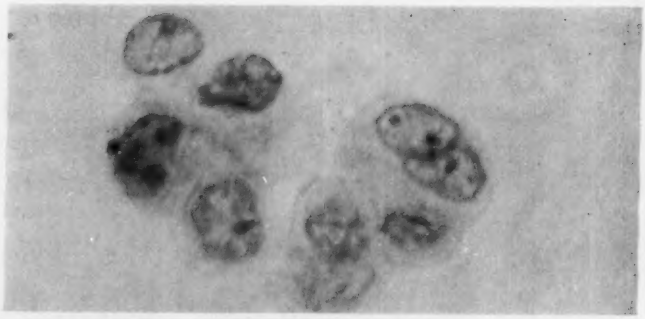
4. The next step consists of having the patient on his right side, head down for five minutes, during which time an additional 15 cm. of tubing is passed.



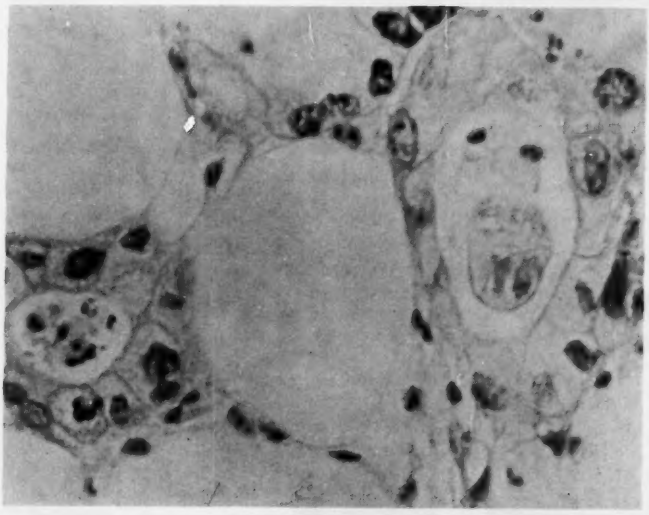
5. The final maneuver facilitates the passage of the tube into the third portion of the duodenum.



6. Duodenal-suction apparatus in use: One unit of secretin per kilogram of body weight is injected intravenously.



7. Well-differentiated adenocarcinoma cells obtained by a duodenal drainage. Tumor originated in the body of the pancreas and did not involve the duodenum.



8. Hematoxylin and eosin stain of biopsy section of the tumor. Note the morphologic similarities between the duct-forming cells and the cells of the preceding photomicrograph.

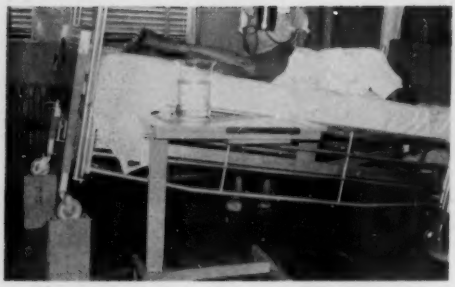
9. Highly anaplastic carcinoma cells, which exfoliated from a carcinoma of the gallbladder.

DUODENAL CYTOLOGY RESULTS

TOTAL CASES - 204

CLINICALLY BENIGN	159	CLINICALLY MALIGNANT	45
CYTOLOGY NEGATIVE	158	CYTOLOGY POSITIVE	30
CYTOLOGY FALSE POSITIVE	1	CYTOLOGY FALSE NEGATIVE	15

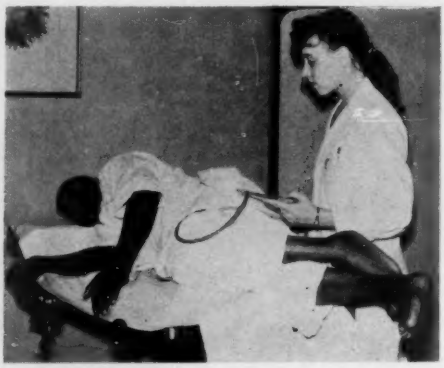
Colonic Irrigation



1. Colon-wash procedure: The patient is given a phosphate cathartic the night before the examination. Multiple isotonic saline enemas are given. Many patients can tolerate 3000-cc. enemas if the foot of the bed is elevated. Before expelling the solution, the patient rotates to his right side in order to irrigate the ascending colon.

2. A proctoscope is passed 20 cm., and an Ewald tube is inserted through the proctoscope, which is then removed.

3. The first diagnostic enema consists of 700-800 cc. of isotonic saline, which gravitates to the transverse-descending colon junction.

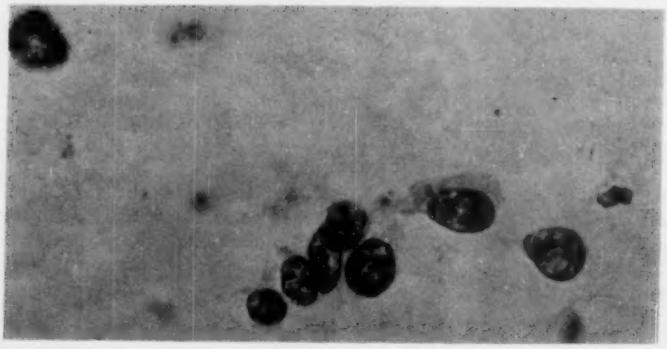


4. The patient lies on his right side to enhance the flow of fluid to the hepatic flexure.

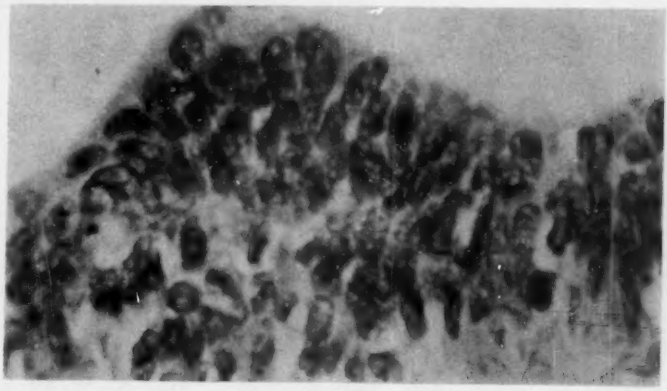
5. The patient rotates to his back, and the abdomen is massaged. Fluid is often balloted in the cecum.

6. Fluid is collected through a strainer into a beaker and then poured into centrifuge tubes. A second diagnostic enema is repeated.

7. Benign colonic columnar cells.



8. A cluster of adenocarcinoma cells obtained from a splenic-flexure malignancy.



9. Histologic section, stained with hematoxylin and eosin, of the splenic-flexure tumor from which the malignant cells in the preceding photomicrograph were obtained.

COLON CYTOLOGY RESULTS

TOTAL CASES - 122

CLINICALLY BENIGN	**97**	**CLINICALLY MALIGNANT**	**25**
CYTOLOGY NEGATIVE	**97**	**CYTOLOGY POSITIVE**	**23**
CYTOLOGY FALSE POSITIVE	**0**	**CYTOLOGY FALSE NEGATIVE**	**2**

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The Analgesic Properties and Addiction Liability of Ketobemidone and Morphine

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Many papers dealing with the clinical use of ketobemidone (Cliradon, Ciba) have called attention to the low potentiality for addiction of this drug. Studies based on large series of cases have shown that patients can give up its use without particular difficulty (Lewis, 1949; Cecchi, 1950; Blanke, 1950; Liessem, 1951; Peltola, 1952). Thus, in spite of fairly extensive use, comparatively few cases of addiction to ketobemidone have been brought to notice. Only in Germany, where the sale of the drug was unrestricted until 1953, has there been a significant number of addicts. There are reports on 20 cases in Germany either of addiction or of misuse (Linder and Vollmar, 1950; Bernmeier and Heine, 1950; Sattes, 1951; Kinzler, 1952; Mühlau, 1952; Cieslak, 1952; Hamburger, 1952; Geller, 1952; Carrière, 1953) and on 4 cases in other parts of the world (Bernstein, 1949; Del Bono, 1952; Peltola, 1952). We may assume, however, that not every case has been reported in the literature, and hence these figures may not be complete. Yet there seems to be no reason to doubt that they do give a fair indication of the incidence of addiction.

In direct contradiction to clinical experience are the results reported by Isbell, in 1949. He made a comparison of five potent analgesics by administering them subcutaneously to 10 former morpine addicts. At the same time, the effects of the drugs were studied with regard to euphoria, abstinence from morphine, abstinence from the drugs under study, and addiction resulting from prolonged use. This author found that ketobemidone, when administered in the same doses as morphine, produced morphine-like euphoria, relieved the symptoms of abstinence from morphine, etc. He concluded that ketobemidone is more addicting than morphine and is, in fact, one of the most addicting drugs yet discovered, while having no advantages over morphine.

Isbell's study, like most other studies of its kind, deals only with doses inducing euphoria and producing psychical and physical addiction, without paying attention to the analgesic dose. Now the primary objective of studies dealing with synthetic analgesics is to find a drug which produces analgesia with doses considerably smaller than doses producing euphoria and addiction, so as to prevent any misuse originating in its clinical application (Goodman and Gilman, 1955). Until a comparison between these doses is carried out, it is not possible to obtain any definite notion of the advantages and disadvantages of the drug. This important point was overlooked in Isbell's study; therefore, the conclusions he arrived at were hardly justified.

This, and the fact that Isbell's results were in contradiction to clinical observations, made a further investigation desirable. We have carried out clinical studies on the analgesic properties and the liability of addiction of ketobemidone and morphine in painful diseases of long duration. Morphine was chosen as a control drug because the actions of this routine analgesic are well known.

Material and Methods

An attempt was made to compare the analgesic doses of ketobemidone and morphine given over periods of short duration, where the treatment

Submitted for publication March 12, 1957.

From the Medical Department of the Kivelä Hospital.

interval was too brief for any addiction to become apparent, and also over periods of longer duration, where tolerance and addiction have time to develop.

The series consisted of 109 incurable cases, mostly cancer patients in the chronic wards of the Kivelä Hospital, admitted because of lack of facilities for treatment at home and because of persistent pain. No one of them had received opiates or potent synthetic analgesics before admission. The drugs under study were administered as analgesics to these patients. The nurses attending these cases had worked in the wards for years and were fully competent for the task. The patients were unaware of the nature and dosage of the drugs administered. Only analgesia, not sleep, was the aim of treatment. Sleep, sometimes taken to indicate complete disappearance of pain, may actually be due to other factors (Denton and Beecher, 1949).

Ketobemidone (4-[3-hydroxyphenyl]-1-methyl-4-piperidyl ethyl ketone hydrochloride) was administered as a 0.75% solution, and morphine, as a 3% solution. Both drugs were given subcutaneously.

The pain-relieving properties of the drugs were studied in a group of 45 cases. One of the drugs was first administered for not more than a week, in order to avoid the development of dependence. During this period, an attempt was made to find out the minimal analgesic dose which could be used for at least three successive days without having to be increased. After this, the patient was treated with the other drug without being made aware of the change. As with the first drug, an attempt was made during a week's administration to find out the minimal pain-relieving dose. In many cases it was possible after a week to return again to the original drug in order to check any changes in the amount of this drug needed because of the progress of the disease. The doses thus determined were considered to be analgesically comparable. In order to get a sufficient comparison, into this group were taken both cases with high and those with low doses of the analgesic from the beginning. To the former group belong mostly cases with a very resistant acute pain caused by cancer metastasing to the spine and causing fractures of the vertebrae.

In order to determine the degree of addiction caused by prolonged use of the drugs, another group, of 39 patients, received one of the analgesics continuously for at least three months. This period of time is considered sufficient (Goodman and Gilman, 1955) for any euphoria-inducing and addicting properties to produce habituation. After this period, the patient was given the other drug in equal analgesic dosage. If the amount of the second drug proved to be too small, the necessary increase in the dose was made within the first week. Apart from the purely analgesic effect, there are, of course, other factors, too, which determine the dosage in these cases, such as tolerance, the ability to relieve symptoms of abstinence, and the like. Naturally, the cases with this duration of treatment were less advanced at the beginning of the hospitalization and the need for analgesic was thus less pronounced than in the former group.

An attempt was made also to find out how much reduction of analgesic effect of ketobemidone occurred with prolonged use of several weeks or even months. Both human and animal experiments have suggested that the pain threshold is changed to some extent under these conditions. In view of this, any variations in the daily requirement of ketobemidone received careful consideration. It is true that the steady progress of the disease also tended to increase the need for the drug. This factor was difficult to assess with certainty. However, it seems that the figures obtained can be used as a rough guide to the development of tolerance.

Results

Analgesic Action.—After a short-term use of morphine (one week at most) in 29 cases, the analgesic dose of ketobemidone was found to be 5.8 ± 0.4 mg., as compared with 18.2 ± 0.9 mg. of morphine. This suggests that the ratio between the equal analgesic doses of morphine and ketobemidone is 3.3 ± 0.2 to 1 as calculated by weight.

Approximately the same proportion in analgesic dosage was found when morphine was administered after a short-term use of ketobemidone in 16 cases. An average dose of 7.2 ± 0.5 mg. of ketobemidone was equivalent to 20.4 ± 1.7 mg. of morphine. Thus the ratio of morphine to ketobemidone is 2.9 ± 0.1 to 1.

Habituation Due to Prolonged Use.—Administration of morphine in 24 cases over a period exceeding three months increased the dosage requirement of ketobemidone considerably. Under these conditions, the average dose of ketobemidone required was 21.2 ± 1.3 mg. This roughly equaled the morphine dose (23.5 ± 1.1 mg.) which had been required; the ratio of morphine to ketobemidone was 1.2 ± 0.1 to 1. The need for ketobemidone was thus some three times greater than after a short-term use of morphine.

On the other hand, administration of ketobemidone over a period exceeding three months in 15 cases produced no changes in the need for morphine as compared with the results obtained with a short-term use of the drugs. Thus, 22.5±1.4 mg. of morphine equaled 7.4±0.5 mg. of ketobemidone. This ratio, 3.1±0.1 to 1, is essentially unchanged when compared with that of the analgesic action.

Development of Tolerance to Ketobemidone During Prolonged Use.—The results show that the need for ketobemidone increases relatively slowly during prolonged administration. Thus, after 12 months of treatment the daily dosage of ketobemidone rose to 29.2±1.7 mg. (21 cases) from 15.4±1.2 mg. a day at the beginning, the ratio being 1.9±0.2 to 1.0. In many of the cases examined, of course, the increase in the dosage of ketobemidone was ascribable to the aggravation of the disease, but in other cases there was also an evident decrease in the analgesic effect of the drug. One subject, with periarteritis nodosa which continued without any noticeable changes in the pain produced, received ketobemidone for more than eight months. The initial daily dose was only 8 mg., while the terminal daily dose averaged 35 mg. In the majority of cancer cases, however, the patients needed only 10 to 25 mg. daily, even in the terminal phase.

A good example of the slow decrease in the analgesic effect of ketobemidone during prolonged use is the case of the managing director of an industrial firm, who received the drug over a period of about eight months for carcinoma of stomach. During the terminal phase of the disease, the daily dosage was approximately 20 to 30 mg., administered orally. The patient carried out the duties of his job up to a week before his death.

Other Observations.—Earlier studies have called attention to the frequent lack of sedative effect of ketobemidone (when administered in analgesic doses) in contrast to morphine (Vara and Kinnunen, 1951; Peltola, 1952). In the present study, this observation was particularly striking when ketobemidone was substituted for the strongly sedative morphine. In spite of obvious absence of pain, the patients required much more attention, were restless, and showed signs of impatience. In the majority of cases, hypnotics had to be administered simultaneously with ketobemidone. Side-effects, such as vomiting and obstipation, were less frequently present than when morphine was used.

Comment

The results of this study show that the analgesic effect of ketobemidone is approximately three times greater than that of morphine, on a milligram-for-milligram basis.

Administration of morphine over a period exceeding three months considerably increased the need for ketobemidone when the latter drug was substituted for morphine. This was no doubt ascribable to the euphoria produced by morphine and to the resulting addiction and cross tolerance to ketobemidone. To achieve the same degree of euphoria with ketobemidone a much greater dosage of this drug was required than was necessary for analgesia. On the other hand, an apparent low grade of tolerance to ketobemidone was noticed when it was given for three months as well as a relative absence of cross tolerance to morphine.

Euphoria is generally accepted as one of the most important factors in the development of addiction (Isbell, 1948 [first reference]; Goodman and Gilman, 1955). Our results suggest that for these two drugs the difference between the analgesic dose and doses producing euphoria and addiction may be considerable. Comparison between these doses of morphine and doses of other common analgesics, on the basis of the literature, makes this point obvious (Tables 1 and 2). The figures appearing in these Tables are derived from several different studies in which the techniques employed were not similar. In all these studies, however, the doses of the drugs used were correlated

TABLE 1.—*Routine Dosage (Subcutaneously) and Analgesic Dosage According to Various Authorities, as Compared with That of Morphine* *

Drug	Routine Dosage, Mg.	Dosage According to Various Authorities, Mg.							Ratio to Corresponding Dosage
		Seevers 1936	Isbell 1948 (2d Ref.)	Troxil 1948	Gross 1949	Denton 1949	Lasagna 1954	This Paper	
Morphine	15–30 15–20	10 (1)	10 (1)	15 (1)	2 (1)	10 (1)	10 (1)	3 (1)	1
Ketobemidone (Cliradon)	7.5				1 (0.5)			1 (0.3)	0.3–0.5
Meperidine (Demerol)	100–150 50–150		100 (10)	150 (10)	9–10 (5)		50–100 (5–10)		5–10
Methadone	7.5–10		5–10 (0.5–1)	10 (0.75)		10 (1)			0.5–1
Diacetyl-morphine (heroin)	2–5	1–2 (0.1–0.2)							0.1–0.2

* Figures in parentheses represent the ratios of the analgesic dose of each drug to the analgesic dose of morphine as determined in the different studies.

with doses of morphine, and hence they are comparable. The relationship of the analgesic to the euphoria-producing dose can be expressed in the form of a fraction, the former being the numerator and the latter, the denominator. The smaller the analgesic dose in relation to the euphoria-producing dose, the smaller the fraction and, therefore, the smaller the danger of addiction. This fraction can serve as an indication of the safe applicability of the drug to clinical use (Table 3). The Table shows that the fraction is smallest for ketobemidone, indicating that this drug should be the safest for routine clinical use. Some drugs, such as methadone, produce euphoria even when administered in analgesic doses. Therefore, when attention is paid to the requirements of clinical routine, the results of the present study and the figures appearing in Tables 1 and 2 can be assumed to give a fairly accurate picture of the real situation.

TABLE 2.—*Doses Producing Equal Degree of Euphoria, in Comparison with Morphine or Substitution Doses for Morphine* *

Drug	Doses Producing Equal Degree of Euphoria (Subcut., Mg.)		Substitution Doses for Morphine		Ratio to Corresponding Morphine Dosage
	Seevers 1936	Isbell 1949	Isbell 1948 (1st Ref.)	This Paper	
Morphine	10 (1)	30 (1)	4 (1)	(1)	1
Ketobemidone		30 (1)		(1)	1
Meperidine		200 (6.5)			6.5
Methadone			1 (0.25)		0.25
Diacetyl-morphine	1–2 (0.1–0.2)				0.1–0.2

* Figures in parentheses represent the ratios of euphoria-producing dose of each drug to the euphoria-producing dose of morphine in each study.

TABLE 3.—*Ratio Between Analgesic and Euphoria-Producing Doses, Compared with Morphine*

Drug	Analgesic/ Euphoric	Ratio
Morphine	1/1	1
Ketobemidone	0.3–0.5/1	0.3–0.5
Meperidine	5–10/6.5	0.75–1.5
Methadone	0.5–1/0.25	2–4
Diacetyl-morphine	0.1–0.2/0.1–0.2	1

The ratio between the analgesic and euphoria-producing doses is not, of course, of decisive importance when one is dealing with the misuse of a drug which has originated outside of clinical application, and it is obvious that the size of that group cannot be kept entirely within control as long as

drugs have euphoria-producing properties.

The results of several studies suggest, however, that misuse is often traceable to the clinical administration of a euphoria-producing analgesic drug (Rasor and Crecraft, 1955). In these cases addiction can obviously be kept within limits by using a drug with minimal euphoria-producing action in analgesic doses.

From the results of the present investigation it seems obvious that ketobemidone, the analgesic dose of which is so much smaller than the euphoria-producing dose, is one of the best analgesics now in clinical use, particularly for relieving pain in illnesses of short duration, where the danger of addiction is of greater importance. For pain attending incurable diseases, such as cancer, where the potentiality of addiction of an analgesic plays no significant role, the use of morphine and its compounds is justified because they produce euphoria even in analgesic doses and thus relieve the patient's psychic distress.

Summary

The object of the present study was to make comparisons between the analgesic and addicting doses of morphine and ketobemidone. Patients with painful incurable diseases were administered both drugs in turn. The substitution of one drug for the other occurred (*a*) after the patient had taken the drug for a week and (*b*) after the patient had taken the drug for three months. The ratio between the dosages in the former case was assumed to depend simply on the analgesic effects of the two drugs, while in the latter case the addiction property of the first drug played a contributory role in the dosage requirement of the substituted drug.

In short-term use, the analgesic properties of ketobemidone were three times more potent than those of morphine on a milligram-for-milligram basis. In prolonged use, morphine caused considerable addiction. The requirement of ketobemidone after prolonged administration of morphine was three times greater than after short-term use of morphine, i. e., required amount (by weight) of ketobemidone was three times greater than the usual analgesic dose and equaled the dosage of morphine. On the other hand, prolonged use of ketobemidone did not result in a corresponding increase in the amount of morphine needed. The fact that the administration of ketobemidone in analgesic doses over a long period did not necessitate any remarkable increase in dosage suggests that the development of tolerance is slow.

The disagreement of these observations with those of some earlier studies is no doubt due to the fact that in the present investigation a distinction was made between the analgesic and the euphoria-producing doses. Comparison of ketobemidone with other common analgesics shows that it is one of the safest drugs to use for analgesia because of the great difference between its analgesic and euphoria-producing doses.

Kivelä Hospital (Dr. Soisalo).

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The Oximeter-Controlled Induced Anoxemia Test

Seventy Tests on Coronary Suspects

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Introduction

The observation that the inhalation of a gas of low oxygen content may bring on angina pectoris, or specific electrocardiographic changes, has led to the induced anoxemia (hypoxemia) test for the study of coronary artery disease.* The type of anoxemia test most widely used is that of Levy and co-workers, in which a gas of fixed low oxygen concentration, 10%, is administered for a period up to 20 minutes.[2]

In two previous papers, with Dr. Caroline Thomas, we described another type of test, the oximeter-controlled anoxemia test,[3,4] in which the content of oxygen in the respired gas is varied to produce the desired degree of anoxemia, measured continuously by the oximeter.[5] This overcomes the large variability in the oxygen saturation of the arterial blood known to result from the inhalation of 10% oxygen and other gas mixtures of fixed oxygen concentration.[3,4,6-8] In subsequent papers, with other co-workers, the following was reported on the oximeter-controlled method:

1. Changes in the electrocardiogram and blood pressure of a large group of young, healthy subjects, at 80%, 75%, and 70% arterial saturation, bore a direct relationship to the level of the saturation.[9] This provided additional justification for standardizing an induced anoxemia test according to the degree of anoxemia.

2. Two new criteria for a positive electrocardiographic response were offered: a depression of the RST segment of more than 1 mm. in any lead and a T wave reversal in Lead I unaccompanied by any RST depression, since these changes were not encountered in normal subjects at 75% (82 subjects) or at 70% saturation (41 subjects).

3. A method of adding carbon dioxide while maintaining a constant degree of anoxemia was described.[10] By eliminating certain side-reactions, e. g., dizziness and hypotension, this method permitted prolongation of some of the anoxemia tests. It also allowed differentiation between responses caused by anoxemia per se and those caused by the loss of carbon dioxide secondary to anoxemia.

4. The oximeter-controlled method was found to be practicable on patients suspected of having coronary artery disease.[11] In a preliminary study of 11 patients, no difficulty was encountered in producing or maintaining the desired degrees of anoxemia.

The present experiments were undertaken to determine the clinical usefulness of the test by applying it to a larger number of patients. Also, the potential value of the ballistocardiogram[12] in the anoxemia test was investigated further, since it had been shown in a previous study[11] that young healthy subjects maintained a normal ballistocardiographic form when made an-

Submitted for publication Aug. 14, 1957.

Vascular Section, Robinette Foundation, Hospital of the University of Pennsylvania.

Presented, in part, at the annual meeting of the Association of American Physicians, 1956.[1]

Supported, at the present time, by the Willard Foundation and, in the past, by the United States Public Health Service and Life Insurance Medical Research Fund (G-51-30).

* For a detailed consideration of the anoxemia test, the reader is referred to the extensive review by Stewart and Carr.[9]

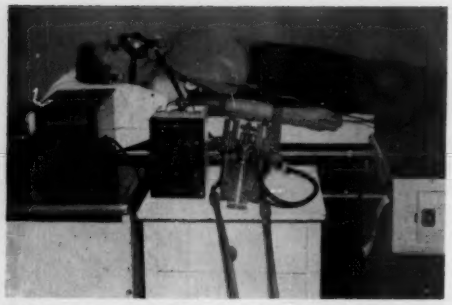

Fig. 1A.—Oxygen-nitrogen gas mixtures are administered through the anesthesia machine, the oxygen content of the mixture being constantly altered to obtain the desired arterial oxygen saturation, measured continuously by the oximeter. The tanks of oxygen and nitrogen are not shown. Reproduced with permission from Penneys, R.: *Tr. A. Am. Physicians* 69:214-221, 1956.

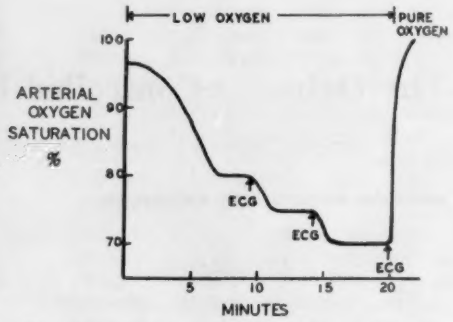

Fig. 1B.—The arterial saturation is lowered in a step-wise manner and stabilized at the desired levels. An electrocardiogram, including multiple precordial leads, is taken at each level, as is a ballistocardiogram. The test is terminated by administering oxygen after reaching 70% to 75% saturation, or sooner, if a "positive" response is obtained at a higher level. Reproduced with permission from Penneys, R.: *Tr. A. Am. Physicians* 69:214-221, 1956.

oxemic, while the form of the coronary suspects usually became abnormal.

Method

Oximeter-Controlled Technique.—The subject rests on the ballistocardiographic bed for approximately one hour (the standard rest period in anoxemia tests), during which time the oximeter earpiece, electrocardiographic leads, and sphygmomanometer are attached (Fig. 1A). Control readings, while the subject is breathing air, are taken. The patient is instructed to signal promptly if he "happens" to have any chest pain during the test but is usually not informed as to the nature of the "breathing test."

The mask is applied, and he is given pure oxygen for one to two minutes to set the oximeter at "100."[8] Then, without his knowledge, nitrogen is added gradually to the inhaled gas and the arterial saturation is lowered in a "stepwise" manner (Fig. 1B). Approximately five minutes is taken to bring the oxygen saturation down to 85% or 80%. Subsequent changes in saturation, usually of 5%, are made in one to two minutes. An electrocardiographic tracing and usually a blood pressure reading are obtained at each level after the saturation has been constant for several minutes. Electrocardiograms are taken almost continuously during the period of maximum anoxemic stress.

The test is terminated by giving pure oxygen after having reached 75% to 70% oxygen saturation, our present lower limit, or sooner if there is a "positive" response, consisting of specific electrocardiographic changes[2,9] (Table 1) and/or induced angina. In a few of the early tests on the coronary suspects the arterial saturation was not brought down to this lower limit, even though the response was still negative, since we wanted to assure ourselves of the safety of each successively lower level of anoxemia. Also, it was not considered worth while to lower the saturation down to 75% or 70% in some of the tests on coronary suspects already having persistent and vague symptoms at relatively high saturations.

The test is not terminated if the form of the ballistocardiogram, which is taken along with the electrocardiogram, becomes abnormal with anoxemia since such abnormalities, alone, are not yet accepted as constituting a "positive" response.

After breathing oxygen and then air, each for approximately five minutes, a final electrocardiogram is taken.

Equipment

Gas Mixtures.—A tank of pure oxygen and a tank of pure nitrogen are attached to an ordinary anesthesia machine, which in turn is connected by rubber tubing to the side-arm of an inspiratory-expiratory valve. The valve is attached at one end to an O. E. M. face mask and at the other end to a breathing bag. The gas is expired into the room air through the expiratory valve on the mask. In addition to these two tanks, tanks containing carbon dioxide are placed in circuit so that carbon dioxide can be added as needed (Fig. 2).

Oximeter.—The Millikan instrument is used. Although this type oximeter gives only relative changes in the arterial oxygen saturation, the saturation can be safely set at "100" on the inhalation of pure oxygen, since the test is not used on patients having any suspicion of a right-to-left shunt in the heart or lungs.[10]

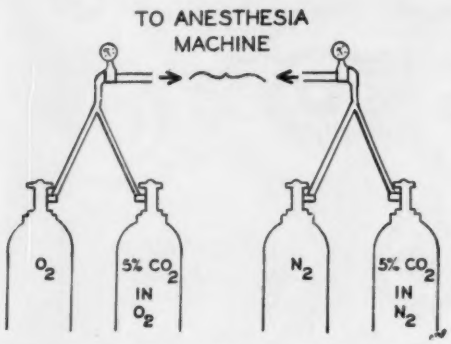

Fig. 2.—The administration of carbon dioxide, at a constant degree of anoxemia, to overcome the effect of carbon dioxide loss secondary to hyperventilation from breathing low oxygen. Five per cent carbon dioxide, shown here, was used for specific experimental reasons.[10] In the routine anoxemia test when the addition of carbon dioxide is necessary, however, lower concentrations of carbon dioxide are sufficient and can be obtained by merely placing a 5% CO_2 and 95% O_2 tank in circuit with the pure O_2 tank. Reproduced with permission from Penneys, R.: *Tr. A. Am. Physicians* 69:214-221, 1956.

Electrocardiograph.—Tracings include the three (bipolar) limb leads and several precordial leads. Chest electrodes are strapped in place, usually in the $C_{3,4,5}$ and 6 positions, so that they will remain unmoved throughout the test. The precordial leads are of the V or CR type. All tracings are taken with a direct-writer. The electrocardiograph is standardized for 1 mv. to give a 1 cm. deflection. The RST deviation is measured from the PQ or P-R segment and not from the T-P segment. This is an important detail since in some tracings the PQ or the P-R segment is significantly lower than the T-P segment.

Ballistocardiograph.—The bed is a horizontal high-frequency Starr type,[12] the tracing being obtained photographically. The ballistocardiographic form is roughly graded as "normal," "slightly abnormal," "moderately abnormal," or "completely abnormal," according to the degree and frequency of appearance of abnormal ballistic complexes.[14]

Subjects

Healthy Subjects.—Ten middle-aged healthy subjects were tested. Normality of these subjects was usually established by a general medical examination, which did not include studies of the blood sugar or cholesterol. Their age averaged 42 years. Six were men, and four, women.

Coronary Suspects.—All of the 65 patients studied were suspected of having coronary artery disease. In a few instances, where the diagnosis of coronary artery disease was certain, the anoxemia test was done to determine the ability of the heart to withstand stress. In most instances, however, the test was used to determine if a pain was due to coronary artery disease. Each patient had a detailed medical examination, including routine laboratory tests and pertinent x-rays. None of the patients had any of the conditions considered to be contraindications to an anoxemia test.[8] In addition, a recent electrocardiogram was required for comparison with the control tracing taken just before the low oxygen was given in order to exclude the possibility of a very recent relatively "silent" myocardial infarction. One such apparent infarction was encountered, and the scheduled anoxemia test was therefore canceled.

Results

The results of 14 tests on healthy middle-aged subjects and of 70 consecutive tests

TABLE 1.—*Electrocardiographic Changes and Symptoms with Anoxemia*

Subjects	Tests, No.	Arterial Saturation (End of Test), %		Positive Electrocardiographic Changes, No. *	Symptoms with Anoxemia	
		Mean	Range		Tests, No.	Type of Symptom
Normal	10	74	70-80	0	0	None
Coronary suspects						
Negative tests	45	76	69-92	0		Pain in "anginal areas" but
					4	(*a*) present on air and not aggravated by anoxemia
					8	(*b*) came on during anoxemia and disappeared without saturation being raised
					2	(*c*) came on during anoxemia and did not disappear promptly with pure oxygen
Positive tests (ECG and/or angina)	25	78	70-87	9 (Criteria 1, 2, or 3) 8 (Criteria 4 or 5)	17	Induced angina
Total	70			17		

* Criteria for positive electrocardiographic response (Criteria 1, 2, and 3 from Patterson, Clark, and Levy [9]; Criteria 4 and 5 from Penneys and Thomas [8]): 1. The arithmetic sum of the RST deviations in all four leads (Leads I-III and a single chest lead) is greater by 3 mm. or more than in the control record. 2. Partial or complete reversal of the direction of the T wave in Lead I, accompanied by an RST deviation of 1 mm. or more in this lead. 3. Complete reversal of the direction of the T wave in a chest lead. 4. A partial or complete reversal of the direction of the T wave in Lead I, in the absence of any RST deviation in this lead. 5. An RST deviation greater than 1 mm. in any lead.

TABLE 2.—*Changes in Ballistocardiographic Form with Anoxemia*

Subjects	Ballistocardiographic Form				
	Air, No. Tests	Anoxemia, No. Tests			
		Normal	Slightly Abnormal	Moderately Abnormal	Completely Abnormal
Normal	14	14			
Coronary suspects					
Negative tests					
Normal	21	17	4	0	0
Slightly abnormal	7	0	4	2	1
Moderately abnormal	11	0	0	8	3
Completely abnormal	1	0	0	0	1
Total	40				
Positive tests (ECG and/or angina)					
Normal	6	2	2	2	0
Slightly abnormal	9	0	0	7	2
Moderately abnormal	5	0	0	3	2
Completely abnormal	0	0	0	0	0
Total	20				

on coronary suspects are summarized in Tables 1 and 2.

Normal Subjects.—No symptoms of any significance were encountered. Changes in the RST segment and T wave of the electrocardiogram did not exceed those previously encountered in the younger healthy subjects.[9] In one 50-year-old subject the RST segment became depressed by 1.5 mm. in leads CR_1 and CR_2 at 70% arterial saturation. The ballistocardiographic form was normal on air and remained normal with anoxemia in all tests.

Coronary Suspects.—Feasibility of the Oximeter-Controlled Technique: No difficulty was experienced in producing, or maintaining, the desired levels of arterial oxygen saturation. The patients were as easy to manage as were the normal subjects.

Symptoms: No serious reactions of any type were encountered. A few patients had transient dizziness. One patient had a severe headache, which came on while breathing low oxygen and lasted for one day but left no after-effects. In seven tests carbon dioxide was added to the low-oxygen gas to relieve complaints of light-headedness or of numbness in the extremities.

Pain located in one of the "anginal areas," coming on clearly with anoxemia and promptly relieved by pure oxygen, thereby fulfilling our requirements for "anoxemically-induced angina," was brought on in 17 of the 25 positive tests. The onset of these pains was between the levels of 87% and 70% arterial saturation. They were kept mild, and brief (one minute or less), by the prompt administration of oxygen.

Symptoms not accepted as "anoxemically induced angina" were encountered in 14 negative tests. Although these symptoms came on while the patients were breathing low oxygen and consisted of some pain or discomfort in the chest, neck, or upper extremities, they were always associated with negative electrocardiograms and dif-

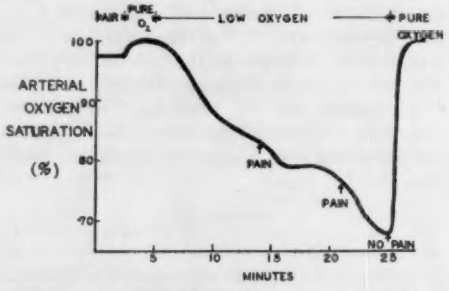

Fig. 3.—Pain not considered anoxemically induced, since it was absent at the lowest saturation, 68%, at the end of the test. This patient's chest pain was atypical in character and clinically was thought not to be due to coronary artery disease; it frequently came on at rest, lasted up to two hours, and was not definitely relieved by glyceryl trinitrate (nitroglycerine). An exercise test was negative, and an electrocardiogram obtained during a spontaneous bout of pain remained normal. The pain at 83% saturation, while the patient was breathing low oxygen, disappeared even before the electrocardiogram, which showed no significant change, was completed. The pain returned very briefly at 77%, and the electrocardiogram again was negative. When the saturation was finally lowered to our limit of 68%, no pain was present and the electrocardiogram remained negative. Reproduced with permission from Penneys, R.: *Tr. A. Am. Physicians* 69:214-221, 1956.

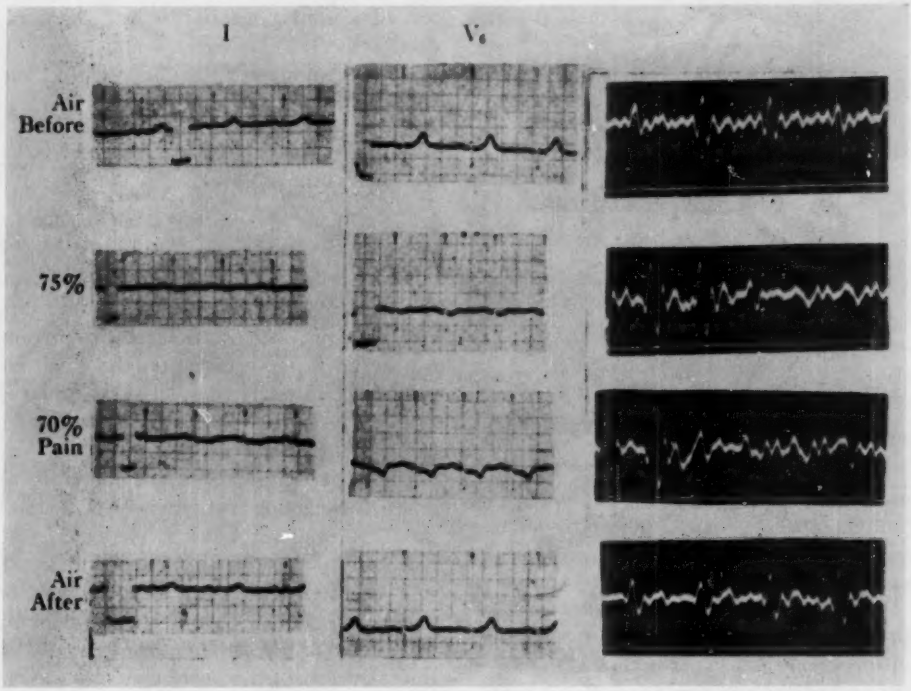

Fig. 4.—Ballistocardiographic changes in a positive test. The ballistocardiogram (on the right) became abnormal at 75% saturation, even before the positive response, consisting of chest pain and inversion of the T wave in Leads I and V_6, appeared. Reproduced with permission from Penneys, R.: *Tr. A. Am. Physicians* 69:214-221, 1956.

fered from anoxemically induced angina in one of several ways: 1. They were already present while the subjects were breathing room air and were not aggravated by low oxygen; 2. they came on while the subjects were breathing low oxygen but disappeared very quickly without the arterial saturation being raised by increasing oxygen in the inspired air, or they did not recur with further lowering of the saturation (Fig. 3), or 3. they came on with low oxygen but did not disappear promptly when the saturation was raised by breathing oxygen at the end of the test.

Electrocardiogram: Seventeen tests showed positive electrocardiographic changes, coming on between 85% and 70% arterial saturation. Nine of these tests were positive according to the criteria of Patterson and co-workers,[2] and the other eight, according to the less stringent standards described by us.[9] The positive change consisted of depression of the RST segment in all tests except one, where it consisted of inversion of the T wave in Leads I and V_6 (Fig. 4).

In eight instances the electrocardiogram remained normal during the attack of induced angina, and in nine cases positive electrocardiographic changes were observed without any anginal pain.

Ballistocardiogram: Tracings were taken in 60 of the tests, 40 negative and 20 positive. The tracing was normal in approximately one-half of the negative tests when air was breathed and usually remained normal on low oxygen. In the positive tests the tracing was normal on air in only one-third of the tests, and in practically all of these it became abnormal on low oxygen, sometimes even before the onset of pain or the appearance of a significant electro-

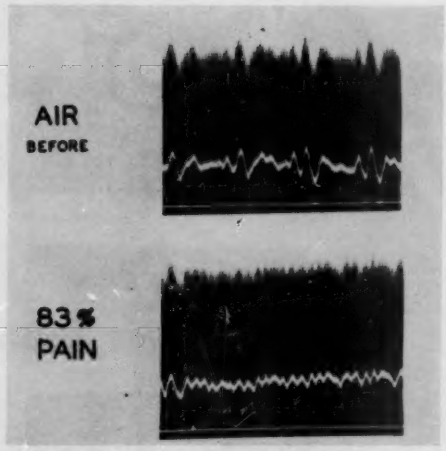

Fig. 5.—The ballistocardiogram during an attack of induced anginal pain; at 83% saturation the tracing is completely abnormal (while the electrocardiogram remained essentially unchanged). Reproduced with permission from Penneys, R.: *Tr. A. Am. Physicians* 69:214-221, 1956.

cardiographic change (Fig. 4). The ballistocardiogram showed striking changes during four attacks of induced angina in the absence of any significant electrocardiographic changes (Fig. 5), but in two attacks it remained normal while the electrocardiogram became positive.

In approximately one-half of the negative tests and two-thirds of the positive, the ballistocardiogram was already abnormal with the subject breathing air, so that the degree of change with anoxemia was more difficult to evaluate. In general, inhalation of low oxygen made the form of the ballistocardiogram somewhat more abnormal in the positive tests than in the negative.

Conclusions

The following conclusions concerning the oximeter-controlled induced anoxemia test for coronary artery disease can be made:

1. It is a practicable test for detecting some instances of coronary artery insufficiency. Tewell and Pritchard [15] and Gürtler et al., with use of a modification of our method,[16,17] have confirmed this. The test requires more personnel and equipment than the 10% oxygen test or the exercise test for coronary artery disease. The duration of the test, however, is not prolonged, since all equipment can be applied, and control tracings taken, during the standard one-hour rest period.

The test offers several advantages over the exercise test [18]: (*a*) The stress is applied without the patient's knowledge, a matter of importance, since coronary "stress" tests are frequently performed on apprehensive patients having unusual pains. (*b*) Tracings, such as the electrocardiogram, can be taken more easily on the quiet, recumbent subject. They can be obtained throughout the period of stress, so that the early abnormalities occurring in the "preanginal" period of stress and those abnormalities occurring for very brief periods during the actual attack of induced coronary artery insufficiency can be detected. (*c*) The complete "dose" of stress can be given in one test; the electrocardiogram, taken with a direct-writer, is examined at each level of arterial oxygen saturation, and if no positive changes are obtained the full anoxemic stress can be given.

2. Certain false-negative tests resulting from insufficient anoxemic stress can be eliminated. Almost one-half of our positive responses were not obtained until an arterial saturation of 75%, or lower, was reached. This level of anoxemia is often not obtained with the inhalation of 10% oxygen.[3,4,6-8] As each progressively lower level of saturation is explored by the oximeter-controlled method, the number of false-negative tests should diminish.

3. Certain false-positive responses can be eliminated, since symptoms experienced by some patients while breathing low oxygen can be shown to be independent of the anoxemic stress. This is of importance because symptomatically positive responses, without any electrocardiographic change, constitute a significant number of the positive tests reported.[8] The relief of some symptoms, such as numbness in the hands, by the addition of carbon dioxide without a change in the degree of anoxemia may

also occasionally prevent such symptoms from being labeled as induced angina.

4. The degree of anoxemic stress necessary to produce a positive test is known, rendering the induced anoxemia test quantitative. The oximeter-controlled test can therefore be used to compare degrees of stress required to produce a positive response in the same, or different, patients.

5. Unduly low levels of arterial saturation can be avoided. This should result in a safer test, although the trained observer should probably be able to terminate any test on the basis of symptomatology alone. Control of the rate of induction of anoxemia should also prevent some untoward reactions.[4]

6. The effect of carbon dioxide on the heart during anoxemia, a matter of physiological and clinical interest,[10] can be more critically evaluated. The ability to keep constant the arterial oxygen saturation after adding carbon dioxide to the low-oxygen gas mixture should allow us, for example, regularly to reproduce Barach and Steiner's single experiment in which addition of carbon dioxide reversed changes in the RST segment of the electrocardiogram of a patient having coronary artery disease.[19]

Our experiments also go one step further in establishing two electrocardiographic criteria for a positive response: a depression of the RST segment greater than 1 mm. in any of the limb or (left) precordial leads and an inversion of the T wave in Lead I unaccompanied by any depression of the RST segment in this lead. The eventual acceptance of these two criteria, already confirmed by Tewell and Pritchard,[15] should significantly lower the number of falsely negative electrocardiographic responses.

Finally, our experiments show that the Starr ballistocardiogram is a useful adjunct in the anoxemia test. Its form remains normal with anoxemia in middle-aged people as well as in young adults [11,20] and in some coronary suspects becomes abnormal with anoxemia before an abnormal electrocardiogram or anginal pain is induced. During some anoxemically induced anginal attacks it may show abnormalities when the electrocardiogram fails to do so. Its final significance in the anoxemia test, however, is not yet established, since normal tracings sometimes become abnormal with anoxemia in the negative tests as well as in the positive. Whether or not the abnormal ballistocardiographic tracings obtained in such negative tests are evidence of some type of myocardial dysfunction is an interesting speculation.

The high-frequency bed appears to be well suited for the anoxemia test, since the ballistic curves are not disturbed by the relative slow respiratory excursions, and the bed is simple to operate. Concina also used a high-frequency ballistocardiogram and has confirmed this.[21]

Summary

The results of 70 oximeter-controlled induced anoxemia tests on patients suspected of having coronary artery disease are reported. The marked variability in the arterial oxygen saturation, such as is encountered when 10% oxygen is inhaled, is prevented by altering the oxygen content of the inhaled gas in order to produce the desired saturation, as measured by the oximeter.

From these, and from previously reported experiments, it is shown that the oximeter controlled test (1) is a practicable and safe procedure, (2) eliminates some "false-negative" and some "false-positive" responses for coronary artery disease to induced anoxemia, (3) makes the anoxemia test a quantitative stress test in that the degree of anoxemic stress necessary to produce a positive response is known, (4) allows measurements, such as the electrocardiogram, to be made throughout the period of stress, (5) allows a more critical evaluation of the effect of carbon dioxide on the heart during induced anoxemia.

Two additional criteria for a positive electrocardiographic response are offered: a depression of the RST segment greater than 1 mm. in any of the limb or (left) precordial leads and an inversion of the T wave in Lead I unaccompanied by any depression of the RST segment in this lead.

Finally, the Starr high-frequency ballistocardiogram is shown to be a useful adjunct in the anoxemia test.

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Illustrated Article

Studies in Headache Mechanisms

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Introduction

Headache may be the commonest complaint heard in physicians' offices. The great majority of headaches are linked either with cranial vasodilatation or skeletal muscle contraction and cranial vasoconstriction. The former are called migraine; the latter, muscle-contraction headache.[1] Changes in gastric function, feeling state, nasal function, fluid and electrolyte excretion, cardiac rhythm, and body temperature regulation may occur in association with headache attack. A part of our newer knowledge of migraine headache phenomenology is herein reviewed.

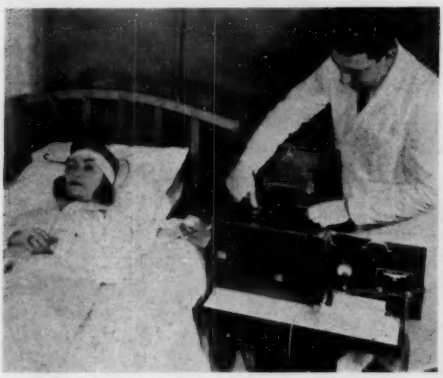


Fig. 1.—Cranial artery pulse wave recorder.

Submitted for publication Nov. 7, 1956.

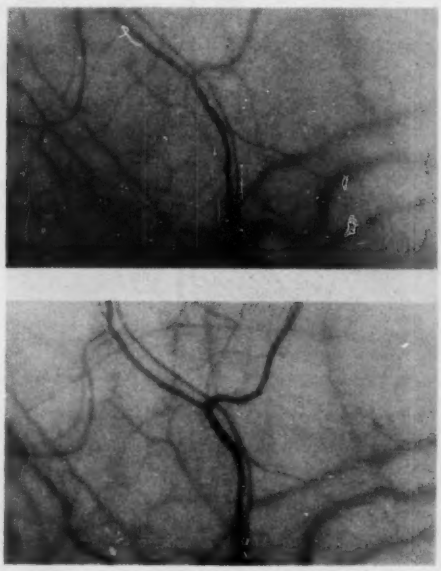
Shown as a scientific exhibit of the Section on Internal Medicine at the 105th Annual Meeting of the American Medical Association, Chicago, June 11-15, 1956.

From the study program in Human Health and the Ecology of Man and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College. Present address of Dr. Ostfeld: University of Illinois College of Medicine.

Fig. 2.—Poser slit lamp and camera attachment for study of bulbar conjunctival vessels.

Headache mechanisms were studied with use of the devices shown in Figures 1 and 2.

Fig. 3.—Effect of topical acetylcholine on bulbar conjunctival vessels. Contrast the normal vessels at the top with the minimal dilatation (sensitivity) at bottom.



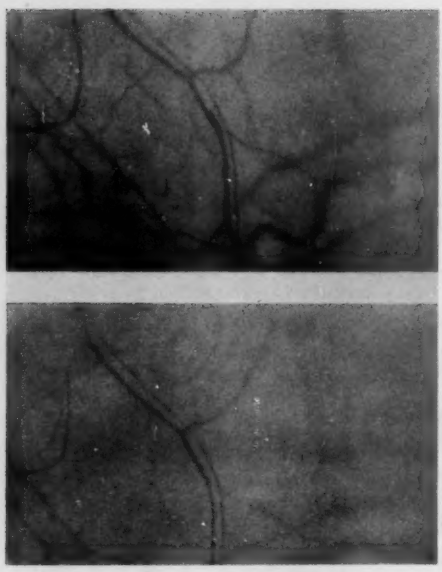
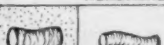
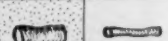


Fig. 4.—Effect of topical levarterenol on bulbar conjunctival vessels. Those at the top are normal. At bottom, the sensitivity to levarterenol is shown. Capillaries are completely blanched.

Fig. 5.—Schematic representation of function and sensitivity to topical arterenol of bulbar conjunctival blood vessels on side of migraine headache.

	INTERVAL PHASE	PRE-HEADACHE	HEADACHE	CORTISONE		72 HRS. AFTER END OF HEADACHE
VENULES						
ARTERIOLES						
CAPILLARIES						
SENSITIVITY TO ARTERENOL	1 TO 100 000	1 TO 500 000	1 : 10 000 TO 1 : 15 000		1 TO 50 000	1 TO 100 000

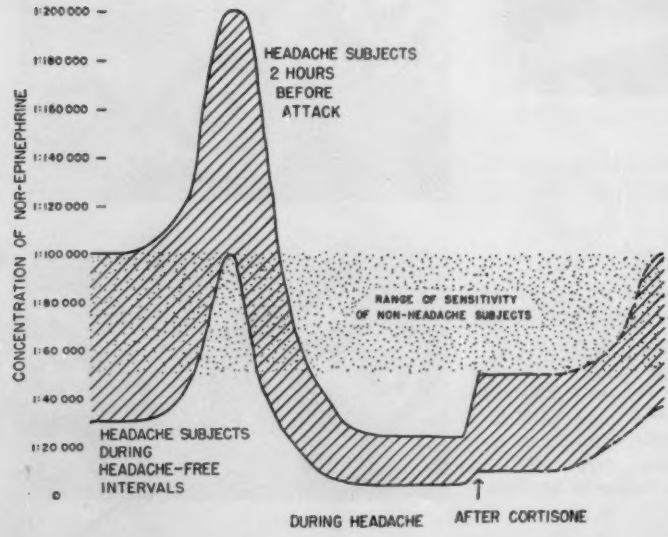


Fig. 6.—Sensitivity to arterenol of conjunctival vessels.

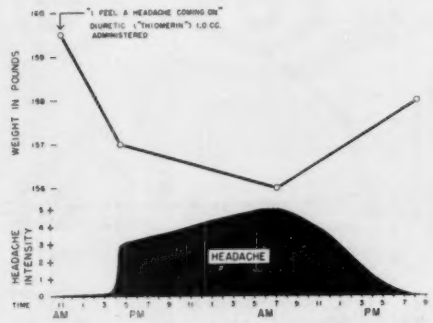


Fig. 7.—Headache and hydration; results of administration of mercaptomerin (Thiomerin).

BODY WEIGHT IN POUNDS
DAYS
OCCURRENCE OF HEADACHE IN MONTH WITHOUT DIAMOX
OCCURRENCE OF HEADACHE IN MONTH WITH DAILY ADMINISTRATION OF DIAMOX

Fig. 8.—Headache and hydration; occurrence of headache with and without acetazolamide (Diamox).

The appearance, behavior, and reactivity of the bulbar conjunctival vessels were determined before, during, and after headache. During the migraine attack, there are local edema and burning pain in the eye in addition to the minute vessel dilatation [2] (Figs. 3 to 6).

Generalized fluid retention, although common in the migraine syndrome, has no relevance to the headache itself. Weight gain may be induced or prevented without

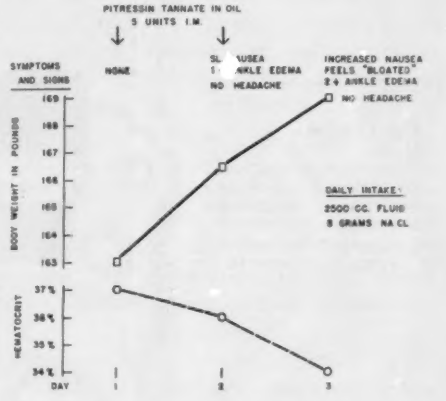


Fig. 9.—Headache and hydration; results of administration of vasopressin (Pitressin) tannate.

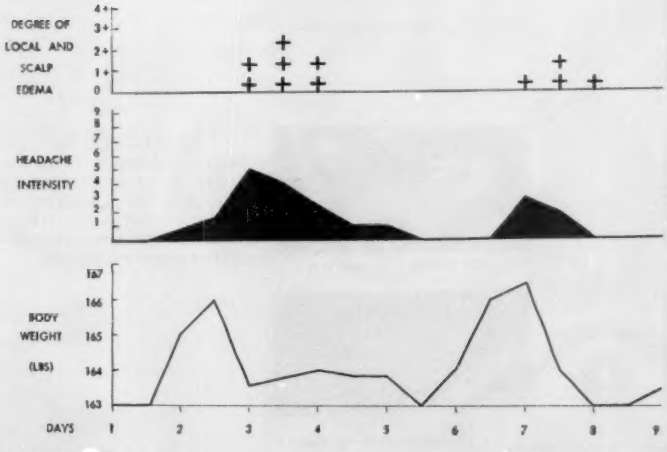


Fig. 10.—Headache and hydration; 42-year-old woman; October, 1954.

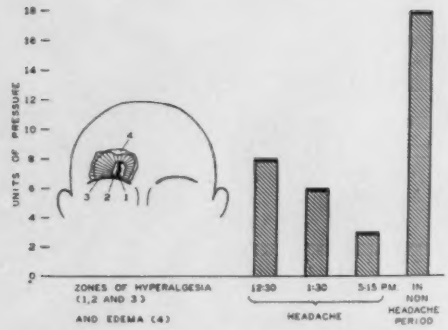


Fig. 11.—Progressively lowered thresholds of deep pain during supraorbital vascular headache.

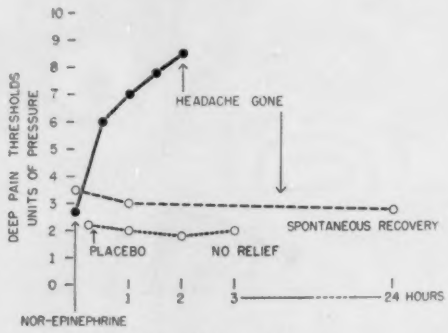


Figure 12

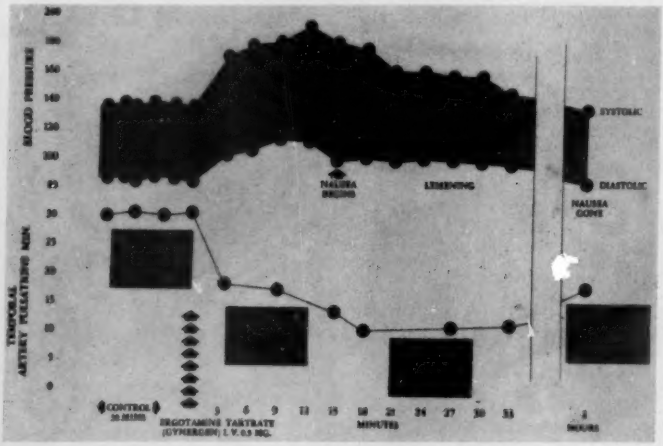


Fig. 13.—Data on a 56-year-old woman with right cervical sympathectomy, showing failure of denervation of peripheral blood vessels to abolish the vasoconstrictor effect of ergotamine tartrate.

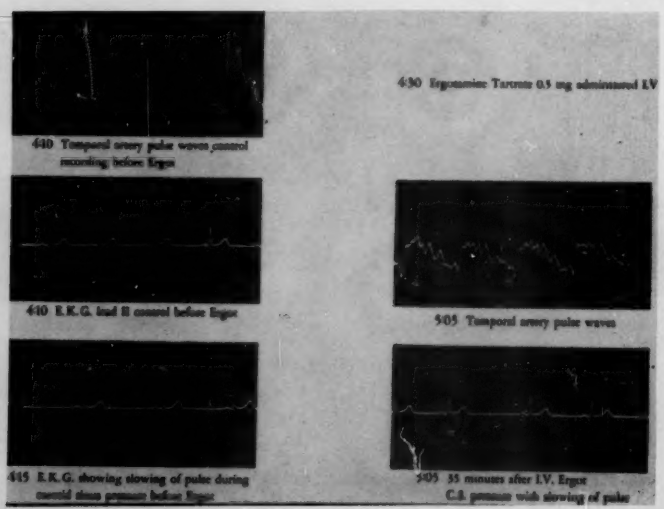

4:30 Ergotamine Tartrate 0.5 mg administered I.V.
4:10 Temporal artery pulse wave, control recording, before Ergot
4:10 E.K.G. lead II control before Ergot
5:05 Temporal artery pulse wave
4:15 E.K.G. showing slowing of pulse during carotid sinus pressure before Ergot
5:05 55 minutes after I.V. Ergot
C.S. pressure with slowing of pulse

Fig. 14.—Data on a 28-year-old man, showing failure of ergotamine to abolish the sensitivity of the carotid sinus reflex, while vasoconstrictor effects are maximum.

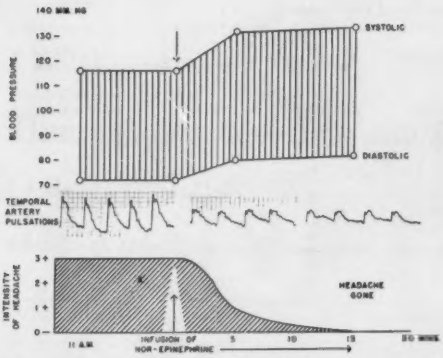


Fig. 15.—Effects of arterenol (norepinephrine). Blood pressure and temporal artery pulsations during elimination of vascular headache.

affecting the onset or course of the headache [2] (Figs. 7 to 9 and Table 1).

Local subsurface edema, a predictable feature of the migraine headache attack, is not related to the generalized fluid accumulation but occurs in areas where deep pain thresholds are lowered. The local edema and lowered deep pain thresholds often outlast the headache but are terminated more rapidly than occurs spontaneously if vasoconstrictor agents are administered [3] (Figs. 10 to 12).

Ergotamine tartrate is effective in alleviating headache, reducing local edema, and raising deep pain thresholds primarily because of its vasoconstrictor effect. In the doses used in the treatment of migraine, it has no other predictable vascular action that would terminate headache.[4] Levarterenol, an agent with almost pure vasoconstrictor and minimal metabolic action, has the same effects in migraine headache (Figs. 13 to 15). Tissue damage, both extracranial and intracranial, may occur at the site of headache. A third-nerve palsy is shown (Fig. 16).

TABLE 1—*Frequency of Fluid Retention in Migraine Headache*

	Total No.	No. with Fluid Retention
By history	134	63
By weight measurement *	51	31

* Sudden weight gain of 2 to 9 lb. (55% gained 3 to 5 lb.) preceding a headache.

Fig. 16.—Third-nerve palsy.

The predictable local occurrence during migraine headache of large and minute vessel dilatation, edema, pain, and lowered deep pain threshold led to the formulation that an agent capable of lowering pain thresholds, causing tissue damage, and augmenting the pain of arterial dilatation collected locally during the headache attack.

Data about such an agent have been accumulated from study of temporal artery biopsy specimens obtained during headache, assay of the effects of saline extracts of subsurface tissue juice and of known pain initiators, and observations on the pharmacology of bulbar conjunctival minute vessels [5] (Fig. 17 and Table 2).

Although all are pain initiators, in all probability the headache substance is not

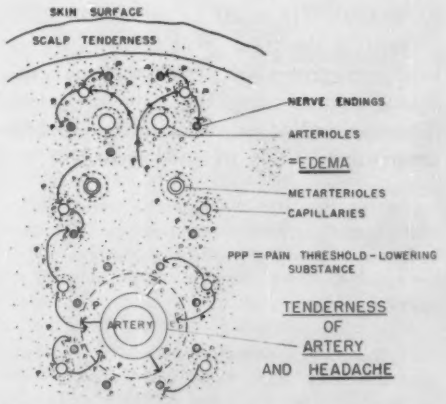


Fig. 17.—Headache mechanisms. 1. At onset of headache, all vessels have dilated. Fluid containing pain-threshold-lowering substance enters tissue and accumulates. 2. Arterenol will constrict all vessels. Fluid and excess pain-threshold-lowering substance drawn back into the plasma.

TABLE 2.—*Comparison of Properties*

	Blister Fluid P. P. S.*	Serotonin	Bradykinin	Headache Substance
1. Pain initiated (superficial and deep)	+	+	+	+
2. Pain duration	Prolonged	Prolonged	Prolonged	Prolonged
3. Vascular headache initiated (under special circumstances)	+	+	+(?)	+(?)
4. Vasodilatation	+	+	+	+
5. Increases permeability	+	+	+	+
6. Lowers pain threshold				
Superficial	+	+	+	+
Deep	+	+	+	+
7. Increases tissue vulnerability	+	+	+	+
8. Contained in ultrafiltrate	+	+	+(?)	+(?)
9. Soluble in water	+	+	+	+
10. Antagonized by atropine	0	0	0	0
11. Antagonized by antihistaminics	0	0	0	0

* Pain Producing Substance

any of the following agents:

1. Histamine (antihistaminics, 0)
2. Acetylcholine (atropine, 0)
3. Potassium or sodium (chemical analysis)
4. Angiotonin—vasoconstriction
5. Leukotaxine (causes cellular reaction)
6. Oxytocin (insignificant vasodilator effects)
7. Vasopressin (vasoconstriction)
8. Necrosin (destroys collagen bundles)
9. The ninhydrin-staining amino acids or simple peptids: methylhistidine, glutathione, carnosine, and anserine

Summary and Conclusions

The tissue changes accompanying migraine headache that occur in the eye and subsurface areas of the head are depicted. As well, the effects of vasoconstrictor agents on these tissue alterations and their nonrelationship to the generalized fluid accumulation preceding headache are shown. Data supporting the thesis that there is present locally an agent which promotes tissue breakdown and enhances the pain of arterial dilatation and observations on the probable nature and effects of this agent are presented.

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Case Reports

Hemoglobin C-S Disease Complicated by Paracolon Osteomyelitis

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Bacterial osteomyelitis has been reported as a complication of sickle-cell anemia. The cases previously described, however, were not studied by newer techniques to differentiate the various hemoglobinopathies. The following case is one of hemoglobin C-S disease complicated by chronic osteomyelitis of both humeri due to paracolon bacilli.

Report of Case

A 29-year-old Negro man was admitted initially to the Philadelphia Veterans' Administration Hospital on May 5, 1954. He had been asymptomatic until 1946, at which time he developed pain in both arms and in the right hip. A diagnosis of osteomyelitis involving the proximal portion of the right femur and both humeri was made. The proximal portion of the right femur and the distal portion of the right humerus were surgically drained. Drainage from the right humerus continued for an eight-month period. Shortly thereafter, spontaneous drainage from the proximal end of the right humerus developed and persisted until admission. He was hospitalized for reevaluation of the chronic osteomyelitis in 1948. At that time, guinea pig inoculation of the exudate from the right humerus was reported to be positive for acid-fast bacilli. Numerous other studies for acid-fast bacilli were negative. A general sense of well being and normal weight had been maintained during the entire course of the illness.

The patient's father died at the age of 55 of a cerebral vascular accident. His mother and six siblings are living and well. One sibling died of tuberculosis.

Physical examination on admission revealed a well-developed and well-nourished Negro man who walked with an obvious limp. There was shortening of the right leg. Well-healed operative scars were found over the right greater trochanter and the right distal humerus. There was a draining sinus from the proximal portion of the right humerus.

Laboratory studies revealed a hemoglobin value of 13.5 gm. per 100 ml. and a hematocrit of 41%. Numerous cultures of the right humeral exudate showed α-hemolytic staphylococci and coliform organisms. Roentgenographic examination of the right humerus disclosed sclerosis of its midportion, with encroachment on the medullary canal. There were two areas of radiolucency involving this portion of the humerus, with a sinus tract to the proximal one.

A course of chloramphenicol was given, with subsidence of the local pain and tenderness but with no effect on the drainage.

Second Hospitalization (Nov. 14, 1956).—After his discharge in 1954, the patient had been completely well, although drainage from the right humerus had continued. In May, 1956, specific antimicrobial therapy for tuberculosis was begun because of suspected reactivation. This was continued until two weeks prior to admission. No bacteriological or radiological evidence to support this assumption was evident. One week prior to admission the patient developed chills, fever, and pain in both arms and the left shoulder.

Physical examination did not differ from that on his previous admission, with the exception of a temperature elevation to 102.4 F and a spleen palpable 3 cm. below the costal margin.

Tuberculous osteomyelitis was felt to be the most likely diagnosis, and accordingly therapy with streptomycin and isoniazid was begun. The patient was symptomatically improved within 24 hours and was afebrile within 4 days. However, the drainage from the right humerus persisted.

Laboratory Studies: A complete blood cell count revealed 6200 white blood cells, with a normal differential; 4,200,000 red blood cells; 13.7 gm. of hemoglobin; 43% hematocrit, and 210,000 platelets. Twenty-two per cent of the red blood cells were target cells. A hemoglobin electrophoresis revealed a C-S pattern, with 53.5% hemoglobin C and the

Submitted for publication Aug. 27, 1957.

From the Medical Service of the Veterans' Administration Hospital.

Fig. 1.—X-ray film of right humerus, showing widespread sclerosis with marked cortical thickening and areas of radiolucency.

remainder hemoglobin S. Alkali denaturation was less than 2%. A sickling test was 3+ with use of sodium metabisulfite. A bone marrow examination revealed erythroid hyperplasia. Numerous smears and cultures from the exudate of the right humerus and sputum and gastric washings were negative for acid-fast bacilli and fungi. The total protein was 7.9 gm. per 100 ml., with 3.9 gm. per 100 ml. of albumin. The serum bilirubin was 1.2 mg. total, with a direct-reading value of 0.1 mg. The cephalin flocculation was 3+ at the end of 48 hours. Febrile agglutinins, serological test for syphilis, and blood cultures were negative. Serum calcium, phosphorus, and alkaline phosphatase were within normal limits. Osmotic fragility revealed a shift to the right (increased resistance). Skin tests with PPD and histoplasmin were negative, and serological studies for histoplasmosis, blastomycosis, and coccidioidomycosis were negative. Cultures of the exudate from the right humerus again revealed α-hemolytic staphylococci and coliform organisms. Differential sugar fermentation studies revealed the coliform organisms to be paracolon bacilli.

Roentgenographic studies revealed the skull, ribs, hands, feet, and lumbar spine to be normal. The dorsal spine showed coarsening of the trabecular pattern, with increased prominence of the vertebral striations. There were biconcave deformities of the lower dorsal vertebrae. There was striking sclerosis of the midportions of the metaphyses of both femora, humeri, forearm bones, and tibiae (Fig. 1). This was the result of marked cortical thickening, which was predominantly endosteal with encroachment upon the marrow cavity. There was aseptic necrosis, with flattening and mushroom deformity of the head of the right femur and severe degenerative arthritis of the right hip joint (Fig. 2).

Electrophoresis of the hemoglobin was done in the patient's family. The patient's mother has hemoglobin AC; one sister has hemoglobin CS, and two other sisters have hemoglobin AA. The father's hemoglobin can be presumed to have been AS (Fig. 3).

Comment

Hemoglobin C-S disease was originally described by Kaplan et al.[1] in three cases

Fig. 2.—Aseptic necrosis of the right femoral head and degenerative arthritis of the right hip joint.

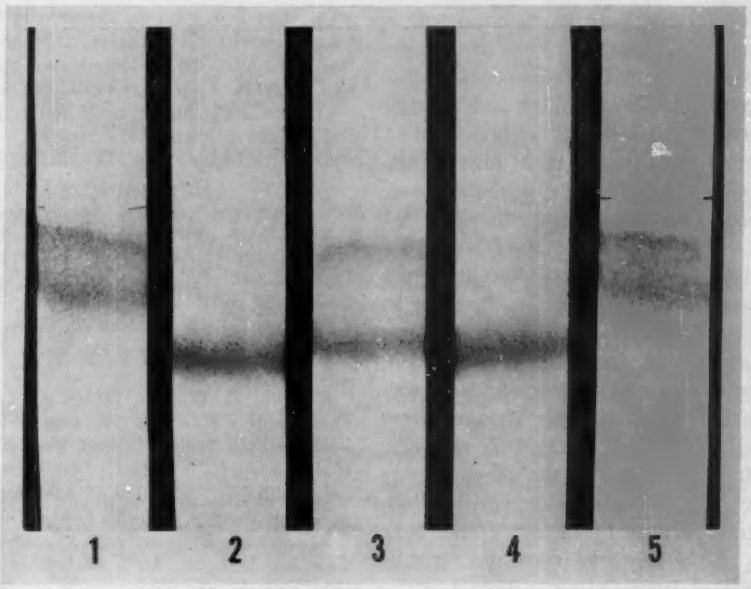

Fig. 3.—Hemoglobin electrophoretic studies of the patient and his family: *1*, the patient (C-S); *2*, sibling (A-A); *3*, patient's mother (A-C); *4*, sibling (A-A); *5*, sibling (C-S).

from two families. Both of these families had parents with AC and AS hemoglobin types. The incidence of this hemoglobin abnormality, which is generally considered to be the commonest of the heterozygous hemoglobin diseases, is 1 in 1500 American Negroes.[2] Its inheritance is probably as a simple Mendelian dominant determined by a single set of allelomorphic genes.

The onset of symptoms in hemoglobin C-S disease usually occurs in the early teens or later, compared with the childhood onset in S-S disease. Smith and Conley [3] reported two cases, one asymptomatic until age 70 and the other still asymptomatic at age 65. Clinically, patients with hemoglobin C-S disease show a mild, chronic, hypochromic, slightly microcytic hemolytic anemia, with a reticulocytosis of 0.1% to 8.0% and other evidences of mild to moderate hemolysis. There is generally progressive splenomegaly, hematuria, polyarthralgia, and abdominal pain. Crises are generally infrequent and mild in nature. They are, however, common in late pregnancy and the postpartum period. Death is not infrequently due to postpartum hemorrhage. The spleen may eventually become infarcted and small as in S-S disease. The defect of the red blood cell is intrinsic, and the red blood cell survival time is decreased. The resistance of the red blood cells to hypotonic saline is increased. Sickling occurs in wet preparations and is of the filamentous type. Target cells are increased and range between 4% and 80%, with the average, 60%. Hemoglobin electrophoresis shows approximately equal amounts of hemoglobins C and S. Hemoglobin F may be present up to 7% but is often absent.

A review of the literature reveals 12 previously reported cases of osteomyelitis complicating "sickle-cell anemia." [4-11] None of these was studied by electrophoresis, and undoubtedly some of them were due to a heterozygous combination of which hemoglobin C-S is the commonest. Although Salmonella osteomyelitis is not common, most of the cases of osteomyelitis complicating the hemoglobinopathies are due to this organism. The frequency seems beyond coincidence, but no reason has been advanced for this observation.

Of the 12 cases previously reported, 8 were due to salmonellae; 1, to a viridans Streptococcus; 1, to Staphylococcus, and 2 cases were not specified. Wigh and Thompson[6] noted a diaphyseal rather than a metaphyseal location in their case. They also noted cortical fissuring in the areas of osteomyelitis and attributed this to sickle-cell anemia.

The bone changes of sickle-cell anemia were summed up by Margolies[12] as due to erythroblastic hyperplasia in the early stages, characterized by irregular trabeculation, widening of the medullary spaces, and cortical thickening. The later changes were presumed to be due to sclerosis and new bone formation, with medullary cavity widening, loss of bone tissue, cortical thinning, and periosteal reaction. The bone changes of the hemoglobinopathies must be differentiated from Caisson's disease, metastatic neoplasm, Paget's disease, Gaucher's disease, hyperparathyroidism, and others.

Tanaka et al.[13] found 6 cases of aseptic necrosis in a group of 51 cases of proved S-S disease. In a group of 72 cases of "sickle-cell anemia" studied by Ehrenpres and Schwinger,[7] 4 had aseptic necrosis—3 of the femoral head and 1 of the humeral head. Smith and Conley[3] noted 4 of the 16 cases of hemoglobin S-C disease with aseptic necrosis.

Summary

A case of hemoglobin C-S disease with little evidence of hemolysis and complicated by the presence of paracolon osteomyelitis and aseptic necrosis of the right femoral head is reported. This is believed to be the first case of osteomyelitis due to paracolon bacillus complicating proved hemoglobin C-S disease.

Dr. Mary Fisher did the roentgenologic interpretation; Harriet K. Richards, B.S., and Esther Harrison, A.B., did the hemoglobin studies, and Dr. Ralph M. Myerson reviewed the manuscript.

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Treatment in Internal Medicine

Treatment of the Deep Mycoses

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Introduction

Histoplasmosis, blastomycosis, coccidioidomycosis, actinomycosis, nocardiosis, cryptococcosis, moniliasis, aspergillosis, sporotrichosis, geotrichosis, and mucormycosis comprise the deep mycotic infections. During the past 10 years significant advances in knowledge concerning their epidemiology, pathogenesis, and treatment have been made. These fungal infections manifest a variety of signs and symptoms, often indistinguishable from those caused by viruses, bacteria, and parasites. The pathogenic fungi should be considered in the differential etiology of both acute and chronic pulmonary infections, skin and mucous membrane lesions, and infections of the brain and blood.

Once suspected, fungal infections can often be readily verified by identification of the organism by culture or direct examination of exudates and biopsy material. The pathogenic fungi are not fastidious and will grow on enriched blood agar and a variety of the more restricted media. Thus, failure to make an early diagnosis in most cases is due to the fact that the physician does not consider the pathogenic fungi in the initial differential diagnosis. However, early diagnosis of these fungus infections is essential if the most effective use is to be made of available therapeutic agents.

Clinical evaluation of antibiotics and chemotherapeutic agents for the treatment of the deep mycoses have been uncontrolled for the most part. Therefore, in this review of available therapeutic procedures, information gathered from experimental in vitro and in vivo tests and from clinical trials will be presented. From this summary the physician faced with the problem of treating a case of one of the above fungal infections may choose the most effective combination of chemotherapeutic and antibiotic agents.

Histoplasmosis

Histoplasmosis is the most frequently observed pulmonary mycotic infection in the east-central United States. The known distribution of this disease has widened from North, South, and Central America to include portions of Africa, Europe, and the Far East. The etiologic organism, Histoplasma capsulatum, is a biphasic fungus which grows as a mycelial saprophyte in the soil and converts to a parasitic yeast-like organism in infected tissue. The spores produced in nature become air-borne and are inhaled, initiating a primary pulmonary infection. Both the mycelial and yeast phases, though slow-growing, can be cultured easily on suitable media. The tuberculate chlamydospore of the mycelial phase is the identifying feature of H. capsulatum.

Pulmonary involvement in histoplasmosis ranges from an asymptomatic minimal infiltrate or hilar adenopathy to diffuse infiltration and consolidation throughout both

Submitted for publication Dec. 9, 1957.

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This investigation was supported in part by a research grant from the National Institutes of Health, Public Health Service, National Institute of Allergy and Infectious Diseases (R. G. E283), and in part by the Seymour Coman Fellowship Fund of The University of Chicago.

lung fields. Histoplasma infections of the lungs are generally self-limiting and heal by resolution or fibrosis and calcification. The discretely rounded persisting infiltrates, classified as "coin lesions" or histoplasmomas, though asymptomatic, are often indistinguishable from malignant lesions. The reinfection form of pulmonary histoplasmosis, characterized by necrosis, caseation, and cavitation in the adult, is being recognized more frequently. The mucocutaneous infection generally is considered to be secondary to a primary pulmonary infection. Fatal disseminated histoplasmosis with widespread invasion of the entire reticuloendothelial system occurs most frequently in children. Secondary infections due to H. capsulatum in patients with lymphomas, sarcoidosis, carcinoma, tuberculosis, and other systemic fungal infections are being observed with increasing frequency.

There is as yet no adequately effective therapeutic agent for the treatment of histoplasmosis. Supportive measures are usually sufficient in the case of primary pulmonary histoplasmosis because of the tendency for this form of infection to be self-limiting. Specific therapeutic procedures are particularly indicated for the treatment of (*a*) persisting symptomatic primary infiltrations, (*b*) chronic pulmonary histoplasmosis with cavitation, (*c*) disseminated infections, (*d*) mucocutaneous lesions, and (*e*) histoplasmosis superimposed on other chronic debilitating diseases.

The most promising agent in the treatment of histoplasmosis is a new antifungal antibiotic, amphotericin B, which has a marked in vitro fungistatic effect against H. capsulatum.[1-6] This agent has been highly effective in the treatment of experimental histoplasma infections in mice in amounts comparable to that employed in treatment of the disease in man.[3,5,7] There were no recurrences of the experimental infections after treatment was stopped.

The results of clinical trials with amphotericin B have just begun to be published and are most encouraging.[6,8-11] Definite improvement and cures have been reported in cases with localized oropharyngeal and acute pulmonary infiltrative histoplasmosis but more particularly in cases of chronic cavitary and disseminated histoplasmosis. Cases of cavitary histoplasmosis treated with intravenous amphotericin B have shown improvement clinically and by x-ray, together with actual sterilization of the sputum.[6] In several cases the course of severe acute pulmonary histoplasmosis has also been altered favorably by intravenous amphotericin B.[6,11] The usual oral daily dosage administered has been 2 to 6 gm. for two to four months, with doses as high as 10 gm. per day for very brief periods only. However, the oral preparation is poorly absorbed from the intestinal tract and is no longer available.[5] The newer amphotericin B (Fungizone) given intravenously or intramuscularly is much more effective.[10] The intravenous preparation is reconstituted in 5% dextrose and given in daily amounts of 50 to 150 mg. intravenously by slow drip over a six-hour period. The maximum daily tolerance dose is 1.5 mg. per kilogram of body weight. The initial intravenous administration of amphotericin B may be accompanied by chills and fever, headache, nausea, and vomiting, but these symptoms tend to diminish as therapy is continued. Intramuscular injection of 20 mg. daily has also been recommended. Duration of therapy in successfully treated cases has varied from several weeks to many months. Further critical scrutiny of amphotericin B is required to better elicit its limitations and indications in the treatment of histoplasmosis.

Sulfonamides have been found recently to alter favorably the clinical course of histoplasmosis, although in the past they were reported frequently to be ineffective or questionably effective in experimental and clinical trials.[12-18] Nevertheless, Hodgson et al.[19] were able to influence favorably the course of a case of generalized histoplasmosis with sulfadiazine administered for 18 months. In restudying the sulfonamides it was found that sulfadiazine, sulfathiazole,

and Sulfapyrazine in particular have been fungistatic to the yeast-phase histoplasma organisms. These drugs were both prophylactic and curative for histoplasma infections in mice.[20] Further in vitro studies have indicated that a combination of sulfadiazine with either nystatin or amphotericin B produced a better therapeutic response in experimental histoplasmosis in hamsters than when the drugs were given individually.[21]

Dr. Amos Christie has stated in a personal communication that he has treated six cases of histoplasmosis proved by culture or biopsy with triple sulfonamides. Three were cases of disseminated histoplasmosis in infants, and three were mucocutaneous histoplasmosis in adults. The adults were given orally 6 gm. daily of the drug. In the infants the blood level was maintained at from 14 to 20 mg. per 100 ml. No untoward reactions occurred, and treatment was given over a period of six to eight weeks. All six cases are now clinically well. The triple sulfonamides combined with methyltestosterone[22] in another clinical trial exerted a beneficial effect when employed to treat a case of extensive oral histoplasmosis. Further evaluation of the sulfonamides in the treatment of histoplasmosis is definitely indicated.

Beta-diethylaminoethyl fencholate (MRD-112) has shown promising antifungal activity in vitro against H. capsulatum.[4,23] Daily intravenous doses of 150 to 600 mg. of the drug have been administered in sufficient numbers of clinical cases for periods as long as two months without toxic manifestations. Such trials have produced successful responses in a few cases of both chronic cavitary and disseminated histoplasmosis, although most reports fail to support the usefulness of this agent.[6,8,24-27] It has been generally established that in a well-developed case of chronic pulmonary histoplasmosis favorable results would not be expected from the use of β-diethylaminoethyl fencholate.

Ethyl vanillate has been found useful as a chemotherapeutic agent in a few cases of histoplasmosis[27-30] but has failed in other trials.[27,31] Generally, it has been noted that this medication produced favorable results only in cases of disseminated histoplasmosis, while the chronic pulmonary type of histoplasmosis was not benefited. Daily doses up to 50 gm. given orally are required for effectiveness. Gastric irritation is a frequent complication. A close check on blood levels of the drug is a wise precaution so that the blood concentration never will rise above 30 mg. per 100 ml., a level that is very close to excessive toxicity. The dosage should be gradually increased in approaching therapeutic levels, and, since the therapeutic levels are not maintained longer than six hours, the daily doses must be given in divided amounts every four to six hours. In vitro studies have shown that H. capsulatum is inhibited by ethyl vanillate concentrations of 20 to 30 mg. per 100 ml.,[28] though when it was tested in mice experimentally infected with histoplasma organisms, no chemotherapeutic effect was demonstrated.[32,33] Ethyl vanillate is far from an ideal therapeutic agent, though when the gravity of the disseminating disease is considered, any agent providing even a slight chance of effectiveness is worth a trial!

Nystatin has shown antifungal activity against H. capsulatum in vitro[34] and a marked favorable in vivo effect in experimentally infected animals when the drug is administered early and in adequate amounts.[35,36] Clinical trials with nystatin which frequently elicit toxic reactions when used intravenously have not produced favorable therapeutic results.[6,8,24,27] However, a recent report of proved oral histoplasmosis cured with local injection of the lesion with nystatin supports its effectiveness.[37] Cycloheximide (Actidione), an antibiotic closely related to nystatin, also has shown in vitro activity against a few species of pathogenic fungi,[38] including H. capsulatum.[39] However, in vitro activity of cycloheximide against histoplasma organisms has not been demonstrated by other authors,[40] and the drug has not been effective clinically in the treatment of histoplasmosis.[27]

The aromatic diamidines have been evaluated as therapeutic agents in H. capsulatum infections because of their apparent success in the treatment of blastomycosis. Stilbamidine and 2-hydroxystilbamidine inhibit the growth of H. capsulatum in vitro.[14,41] Very questionable results have been obtained in the treatment of human cases of histoplasmosis, and it is currently felt that no therapeutic response can be expected from these drugs.[6,8,24,27,42] An occasional report has substantiated some therapeutic value of propamidine and 2-hydroxystilbamidine in the treatment of localized oral histoplasma lesions.[24,29,43]

Various sex hormones in experimental fungus infections have been therapeutically ineffective or, even as in the estradiol treatment of mice infected with H. capsulatum, might shorten the survival time of the infected animal.[44] However, in vitro assays of 12 steroids have shown that testosterone, methyltestosterone, testosterone propionate, diethylstilbestrol, progesterone, and estrone possess good fungistatic activity against H. capsulatum.[22,45] One report of a clinical trial of methyltestosterone combined with triple sulfonamides in the treatment of disseminated histoplasmosis demonstrated questionable success in short-term follow-up[22]; another case did not respond to testosterone.[24]

Of other antibiotics tested, penicillin and streptomycin have been completely ineffective.[14,46,47] In fact, streptomycin in vitro has enhanced the growth of H. capsulatum in the mycelial phase,[48] though no increased virulence has been shown in experimental infection with the yeast phase.[49] Ascosin, though effective in experimental histoplasmosis in mice, is too toxic for human use.[50] A new antibiotic, Nepera 1968, has prolonged the survival time in H. capsulatum-infected mice[51] and demonstrated in vitro effectiveness against the organism.[4] Candicidin, also too toxic to be used for treatment in humans, has been found to be very fungicidal as well as fungistatic against H. capsulatum in vitro[4] but only partially protective in its effect on histoplasmosis in mice.[52] Eulicin[53] and anisomycin[4] have proved to possess very good in vitro inhibition of growth of H. capsulatum in low concentrations.

Numerous chemical preparations have been used unsuccessfully in the treatment of histoplasmosis. Iodides and thymol have shown no in vitro or in vivo effects.[12,13] Vitamins, quinine, emetine, aminopterin, urethan, chlorinated hydrocarbons, and aminosalicylic acid have shown no effect on the growth of H. capsulatum or in treatment.[54] Experimentally, quinacrine (Atabrine) was suppressive rather than lethal to H. capsulatum in in vitro testing, but the inhibiting dosage was much higher than the tolerated dose.[54,55] A questionably favorable clinical result has been achieved with its use.[17] Neoarsphenamine has in vitro effectiveness, although at levels considered toxic to man[14]; stibophen (Fuadin) and stibamine glucoside (Neostam) were ineffective against H. capsulatum by in vitro and in vivo methods.[13,14] Antihistaminic compounds have been somewhat suppressive to histoplasma growth in vitro.[56] Vitamin K (Synkayvite), recently has been shown to be particularly inhibitory to H. capsulatum in vitro, although in vivo studies in infected mice proved the drug to be very toxic.[57] Some azomethines related to *p*-aminobenzoic acid have rather high in vitro fungistatic potency against H. capsulatum while exhibiting low toxicity in mice.[58] The aldehyde, piperonal, was the most effective of the azomethines in vitro, but no experimental observation in animal or human has ensued. Disulfiram (Antabuse) has been found effective against H. capsulatum in vitro, though experimentally infected mice were not protected by its use.[59,60] A clinical trial of this agent for 30 days produced no toxic effects, nor was it effective against the Histoplasma infection.[24] A chemical bistertiary amine (Amebacide) seemed promising because of in vitro effectiveness,[4] but therapeutic trials on 14 cases of cavitary histoplasmosis treated with 45 to 300 mg. daily by mouth for three months were failures in all except

possibly 1 case.[6] Disulfiram has had no clinically favorable effect in several trials, but 1,2 bis(*p*[*n*-hexyl methylaminomethyl] phenoxy) ethane dihydrochloride has produced negative sputa in a case of bilateral pulmonary histoplasmosis.[8] Rhodanine and many of its derivatives have been tested in vitro and found quite effective against the histoplasma organism, though toxic to mice when tested in vivo.[59]

Steroid therapy has been scrutinized carefully. Cortisone has caused wider and more rapid dissemination of the histoplasma organism in several animal experiments,[61-63] but Baum et al.[64] could show no influence by steroids on dissemination in infected mice. However, it has been conjectured that cortisone served to contribute to the clearing in several cases of acute pulmonary histoplasmosis, with exacerbation of the lesions occurring after discontinuation of the cortisone.[65,66] In contradistinction, a rapid clinical progression of the disease occurred in another case where cortisone was given for exfoliative dermatitis.[67] Temporary improvement has been noted with the administration of cortisone and corticotropin (ACTH) in some instances, but generally after discontinuation of therapy there has been relapse and widespread dissemination.[68] The treatment of chronic histoplasmosis with steroids, particularly when antibodies to the disease are absent, as well as the continuation of steroids used for a primary disease upon which histoplasmosis is superimposed, requires careful judgment.

Surgical resection of old pulmonary fibrocaseous cavitary apical lesions has been notably successful in removing a focus of infection that may be debilitating and threatening to the patient. Segmental resection and lobectomy have been performed on an adequate number of patients to prove the efficacy of these procedures in selected cases of chronic pulmonary histoplasmosis.[19,27,69-79] MRD-112 as an adjunct to surgery has been advocated,[74,76] but amphotericin B and sulfonamides will probably become the drugs of choice to accompany surgical intervention.

Summary.—At the present time the antibiotic, amphotericin B, administered intravenously or intramuscularly appears to show the most promise in the treatment of mucocutaneous and pulmonary cavitary histoplasmosis. Amphotericin B along with the triple sulfonamides have been shown to affect favorably the course of disseminated infection in the infant and adult and deserve further careful clinical trial. Surgical resection of pulmonary cavitary lesions in selected cases has been successful. The use of the above agents with surgery would seem to provide the patient with the best therapy.

The above review offers many potentially valuable therapeutic agents which should be employed in case amphotericin B is shown not to be successful in the treatment of histoplasmosis.

It is difficult to evaluate the place of steroids in the treatment of histoplasmosis. They have no fungistatic effect on the organisms but may relieve the immediate toxic effects in the acute stage of illness. It would appear to be rational to always employ amphotericin B at the time steroids are administered. When the latter are employed they should be given in full therapeutic doses for only a short time, while the antibiotics must be given for several weeks to months. In acute pulmonary histoplasmosis the disease is usually self-limiting and the rule is for recovery to occur without benefit of antibiotic or drug therapy. This should be kept clearly in mind when potentially hazardous drugs such as the steroids are employed.

Blastomycosis

North American blastomycosis is a chronic granulomatous disease caused by Blastomyces dermatitidis, a diphasic fungus that grows in tissue as budding yeast-like organisms and on laboratory media as a typical conidia-bearing fungus. The natural geographic distribution of the disease com-

prises the whole of the North American continent, but the majority of cases have been reported from the southeastern and north central parts of the United States. However, increasing numbers of cases of blastomycosis are being reported from other locations in the United States and in various parts of the world. The exogenous source of this fungus is probably the soil, but it has never actually been cultured from soil or other sources in nature. The mode of infection is primarily via the respiratory tract and occasionally the skin.

The blastomyces fungus causes cutaneous and systemic infections, the latter progressing to involve the lungs, internal viscera, and bones. The lesions are granulomatous and frequently characterized by suppuration and ulceration. Recent observations suggest that many mild primary benign pulmonary forms of blastomycosis occur in addition to the more rare generalized fatal form. In this respect the infection resembles histoplasmosis and coccidioidomycosis. Both pulmonary and cutaneous forms of the disease may persist as chronic illnesses without serious disability to the patient. Spontaneous healing has been known to occur without benefit of therapy.[80-82]

The aromatic diamidines are the drugs of choice for the treatment of blastomycosis. All forms of the disease generally respond favorably to these drugs. The unusual effectiveness of Propamidine and other diamidines against B. dermatitidis was first tested and proved in vitro.[83-86] Of the diamidines, aminostilbamidine showed the greatest inhibition; stilbamidine, 2-hydroxystilbamidine, and propamidine were equally highly effective in in vivo tests.[41,85,86] Stilbamidine employed in the treatment of blastomyces infected mice favorably influenced pulmonary infection but not infections of the central nervous system.[85,87] The first successful clinical trial with stilbamidine and propamidine in the treatment of a case of generalized blastomycosis was reported in 1950.[88] Soon there followed a report of the successful treatment of three other cases of blastomycosis, who were given 4.5 to 6 gm. of stilbamidine intravenously in two to three courses.[89] Since then numerous case reports of successful treatment of blastomycosis with one of the diamidines have been published.[81,90-110] The average total dose of stilbamidine used in the treatment of most cases has been 3 to 6 gm. given intravenously in several courses to avoid toxic manifestations, particularly trigeminal neuropathy. In some cases total doses of 20 gm. or more of stilbamidine have been administered. The optimum dosage has yet to be determined, since failures have occurred with the above schedule of therapy. From 150 to 300 mg. of stilbamidine has been given daily over long periods of time without toxic effect.[110] The drug is dissolved in 5% dextrose or isotonic saline and administered intravenously as a slow drip. Three or more courses of daily treatment for a period of 10 to 15 days alternating with rest periods of the same duration or continuous therapy for a month or more may be given. Circulatory collapse can result from too rapid administration. The drug is contraindicated in renal or hepatic disease because of its toxic effects on these organs.

Toxic neuropathy has appeared in many cases treated with stilbamidine and is associated more frequently with excessive dosage. Neuropathy occurs usually one month or more after therapy has stopped. Stilbamidine may persist in the tissues for several weeks to months, and it has been shown that ultraviolet light causes this drug both in the bottle and in tissues to change into toxic products. Toxic reactions during and following the use of stilbamidine can be avoided if the drug solution is protected from bright sunlight at all times and if the patient avoids direct exposure to sunlight during and for several weeks after therapy is discontinued.

The use of 2-hydroxystilbamidine, a more stable and less toxic diamidine compound, has proved even more successful as a therapeutic agent for systemic blastomycosis.[6,8,82,103,107,109,111-113] The usual total dosage of of 2-hydroxystilbamidine is 9 to 12 gm. given in daily intravenous amounts of 225

mg. to 450 mg. in single or divided courses.

A few cases of blastomycosis have not responded to stilbamidine or 2-hydroxystilbamidine therapy.[108,110,114,115] The organisms from such cases generally have been found to be drug-resistant. Increasing the daily dose of the specific diamidine used in such cases has not given a favorable response. It is at such times that another form of therapy is highly desirable, and amphotericin B may prove to be the answer. Amphotericin B has been shown by in vitro tests to inhibit markedly the growth of B. dermatitidis.[5] Preliminary studies on the treatment by both oral and intravenous routes of blastomycosis in man with amphotericin B have shown excellent results in the cutaneous, pulmonary, and disseminated illnesses.[9,10]

Potassium iodide was first suggested as therapy for cutaneous blastomycosis in 1894, by Gilchrist, and has been used widely since that time. However, the use of potassium iodide in the treatment of pulmonary or disseminated forms of this disease is open seriously to question.[81,108,116,117] Potassium iodide has no suppressive activity against the growth of B. dermatitidis,[118] and it is thought that the therapeutic responses are probably due to the high content of iodine in the blood.[119] Of the many reports in the literature, only one gives successful results on a small series of systemic cases with oral and aerosolized iodide therapy.[120] Only partial healing of skin lesions due to B. dermatitidis has been the rule with iodine therapy thus far.[103]

Desensitization with autogenous vaccine before initiating iodide, x-ray, or surgical therapy of blastomycosis has been strongly recommended to date.[119,121-123] Such a painstaking administration of iodides with desensitization leaves much to be desired in therapy. Although a few cures of blastomycosis with these procedures have been reported, such therapy in the treatment of systemic blastomycosis has failed to lower the mortality rate below 90%.[124-127] As advocated by Conant et al., desensitization is performed on a patient if skin test sensitivity to blastomyces antigen is sufficiently positive to produce a strong skin reaction.[123] A heat-killed yeast-phase vaccine or blastomycin prepared from a broth filtrate of B. dermatitidis may be used for desensitization, as outlined by Smith.[60]

X-ray therapy has been employed with success in treating early cutaneous lesions,[128] but is best utilized with other forms of therapy. Roentgen dosage varies with the nature of the lesion.[128,129]

Countless other agents and methods have been tried in the treatment of blastomycosis with variable, though generally unimpressive, results. Necarsphenamine, bismuth subsalicylate, methenamine (Urotropin), glucosulfone (Promin), iodochlorhydroxyquin (Vioform), thymol, sulfanilamide (Prontylin), chiniofon, artificial fever, immune serum, whole blood, Trichophytin vaccine, ultraviolet, tripelennamine (Pyribenzamine), dimercaprol (Bal) and mechlorethamine hydrochloride (nitrogen mustard) have all been employed without effect.[103,108] Colloidal copper sulfate[130] and ether[131] have been reported as successful therapeutic agents, but these findings have not been verified. In vitro effect of sulfonamides and triple sulfonamides against B. dermatitidis has been noted as slight, with no appreciable additive effect from methyltestosterone.[22,132] Of the antibiotics, penicillin in large doses generally has not influenced the course of systemic blastomycosis,[103,108] although one case successfully treated with penicillin has been reported.[133] While receiving streptomycin and aminosalicylic acid two patients were reported to have had remissions of their blastomycotic infections.[105] Also, while receiving chlortetracycline (Aureomycin) therapy, two patients with systemic blastomycosis appeared to be improved, but this antibiotic did not effect a cure.[134] Other therapeutic trials with chlortetracycline have been ineffectual,[91,96] as have oxytetracycline (Terramycin) and chloramphenicol (Chloromycetin).[103]

A new antifungal antibiotic, Eulicin, has produced inhibition of B. dermatitidis in

vitro at low concentrations and protected mice against experimental blastomycotic infections [53] following intraperitoneal, intramuscular, and oral administration. Eulicin when compared with stilbamidine, 2-hydroxystilbamidine, nystatin, and candicidin was equal to candicidin in protecting infected mice with much smaller drug concentrations than were nystatin or the diamidines. Candicidin activity against B. dermatitidis by tissue-culture methods was marked.[4] Oligomycin,[135] β-diethylaminoethyl fencholate (MRD-112),[4,23] candidin,[136] and anisomycin [4] have all demonstrated in vitro activity against B. dermatitidis, but clinical trials with the first two agents have been unrewarding.[103,108] Nystatin has effective antifungal activity against B. dermatitidis in vitro, but cycloheximide does not.[34,40] Ethyl vanillate,[103,127] cortisone,[92,96] and corticotropin [103] are of no value. Cortisone is probably contraindicated in the treatment of chronic blastomycosis because it suppresses host resistance and promotes dissemination of the disease.

Diethylstilbestrol, methyltestosterone, testosterone, and testosterone propionate have shown complete fungistasis in in vitro tests against B. dermatitidis but were ineffective in the treatment of experimentally infected mice.[22,92,137] Regression of cutaneous blastomycotic lesions in two patients treated for carcinoma of the prostate with diethylstilbestrol have been reported.[92] The fungistatic effect of sodium propionate against B. dermatitidis has been demonstrated by Keeney.[138] Sodium caprate and sodium undecylenate have also been shown to be promising fungicides.[139] Undecylenic acid showed suppression of growth at concentrations of 10 mg. per 100 ml. against four strains of B. dermatitidis.[140] Oral undecylenic acid treatment of a patient with a disseminated blastomycosis after pneumonectomy has been successful. An oral dose of 5 gm. per day with rapid increases to a maintenance dose of 10 to 25 gm. daily for an average duration of 40 weeks gave encouraging results.[106] While several nitrostyrene derivatives were completely inhibitory to the growth of B. dermatitidis in vitro, animal protection experiments and a clinical trial with these drugs in a case of blastomycosis have failed to demonstrate effectiveness.[141]

Pulmonary resection of the lung lesions due to blastomycosis has gained increasing support. Surgical intervention in blastomycosis is similar to that in tuberculosis, where chemotherapy alone often does not eradicate the focus of infection. Thus, chemotherapy combined with surgical resection for the chronic localized lesion provides the maximum chance of recovery, as suggested by Buechner et al.[142] Successful results with surgical therapy have resulted only when the cases were carefully selected.[72,81,105,106,122,140,142-145]

Pulmonary resection, or biopsy, in unsuspected cases of blastomycosis is hazardous. Diamidine therapy should be started vigorously following such procedures. Kunkel et al.[81] have suggested that pulmonary resection for blastomycosis be done when the disease is (*a*) limited to one lung, (*b*) etiologically proven by culture, (*c*) without clinical evidence of dissemination, and (*d*) present for more than two months with evidence of chronicity or an inability to heal by fibrosis and resolution after an adequate course of chemotherapy.

Incision and drainage, curettage, or excision of peripheral blastomycotic lesions localized in skin, bone, or viscera have been advocated.[127] Such lesions may themselves act as foci for further dissemination, cause disfigurement, or promote epidemiologic spread.

Summary.—A wide variety of drugs and antibiotics have been employed in the treatment of blastomycosis. Thus far the aromatic diamidines, particularly 2-hydroxystilbamidine by intravenous administration, are superior to all other agents. The new antibiotic, amphotericin B, also holds promise of being an effective agent for the treatment of this disease. Surgical procedures for removal of localized chronically active lung lesions combined with chemotherapy have

an important place in the therapy of pulmonary blastomycosis.

The iodides and x-ray therapy are of dubious value in the light of the excellent results obtained by the above procedures. Steroids have no apparent place in the treatment of acute or chronic blastomycotic infections.

Coccidioidomycosis

The saprophytic phase of the organism, Coccidioides immitis, productive of the highly infectious arthrospores, has as its endemic habitat the arid soil of the southwestern United States. Inhalation of such air-borne spore-laden soil causes primary pulmonary infections called coccidioidomycosis, a most important mycotic disease of the southwestern United States. The parasitic form, characterized by spherules containing many endospores, is the tissue phase of C. immitis. This fungus cultured on routine laboratory media will produce only the mycelial phase, appearing as fluffy-white colonies in which the septate hyphae develop into rectangular arthrospores.

The primary pulmonary infections are generally asymptomatic and self-limiting and necessitate no other treatment than supportive measures and close observation to assure localization of the lesion. Approximately only 30% of the cases develop symptoms. Occasionally the fungus spreads from the lungs to other organs. In such disseminated cases the mortality may be as high as 50% to 60%. Dissemination of coccidioidal infections occurs 25 times more frequently in the dark-skinned races than in the white race. Among the whites, dissemination occurs in less than 0.5% of cases. Pregnant women are also more susceptible to coccidioidal dissemination than nonpregnant women of both races.

Chemotherapeutic agents and antibiotics are indicated particularly (*a*) in primary coccidioidal infections occurring in the dark-skinned races and pregnant women, (*b*) in all disseminated infections, and (*c*) as prophylaxis during surgery for removal of residual pulmonary lesions. For the treatment of coccidioidomycosis a wide range of antibiotics and drugs have been evaluated experimentally and therapeutically without definitive success.

Amphotericin B appears to be a most promising antibiotic for the treatment of coccidioidomycosis. It possesses a high degree of activity in vitro and in vivo against C. immitis.[1,5] Mice infected with the coccidioides fungus were protected by the oral or intraperitoneal administration of amphotericin B, but the organisms were not eradicated from the tissues. It has been suggested that amphotericin B is fungicidal when given early in the infection but only fungistatic if given later. The difference in action of the drug on the early and late lesions may possibly be explained on the basis of difference in pathology. Even though amphotericin B was discontinued in the course of animal infections, suppression of the coccidioidomycosis continued, probably indicating that sufficient time for the development of the host defense mechanisms had been provided by the drug. Encouraging results with amphotericin B in the treatment of coccidioidal infections in man have been reported recently. A total oral dosage of 200 gm. of the antibiotic over a three-month period resulted in a cure of a chronic coccidioidal granuloma of the face.[146] Oral therapy in another patient failed.[5] Definite improvement clinically and roentgenographically have been noted in other cases of disseminated and localized disease treated with intravenous amphotericin B.[9,10,147] As has been stated, only the intravenous or intramuscular preparations of amphotericin B are now available.

The antifungal agent, nystatin, inhibits the growth of C. immitis in vitro.[34,148,149] However, studies show that while nystatin is suppressive in moderate concentrations to the growth of C. immitis when added to the cultures early, much larger concentrations were necessary for inhibition when the drug is added after growth is well advanced.[150] Treatment of experimentally induced coccidioidal infections in mice with nystatin reduced the mortality significantly.[149-158]

Mortality was lowest in those animals receiving the antibiotic early and in the largest total dosage. However, all treated animals regardless of time and amount of drug given had disseminated lesions when killed. Poor absorption of nystatin from the gastrointestinal tract limits its usefulness in man, and intramuscular or intravenous preparations on initial administration cause fever, chills, vomiting, and malaise. Daily intravenous doses of 50,000 to 400,000 units have been given for long periods to six patients with disseminated coccidioidomycosis.[6,8,153] Three showed improvement No effect was noted when meningeal involvement was present. The oral preparation has been used in 10 patients with disseminated disease in dosages as large as 12 gm. daily, resulting in one apparent cure.[153] It is currently thought that nystatin will have very limited usefulness in the treatment of coccidioidomycosis.

Because of the promising results in other disseminated mycotic infections, stilbamidine has also been tested in coccidioidomycosis. Of 37 other various compounds tested against three strains of C. immitis for inhibition of growth, stilbamidine was the most effective, inhibiting growth completely in low concentrations.[154] However, as demonstrated by others,[155,156] the inhibitory effect in vitro of stilbamidine and 2-hydroxystilbamidine against C. immitis have shown the need for concentrations too large to be used practically. In vivo trials of 2-hydroxystilbamidine [156] and aminostilbamidine [157] in infected mice demonstrated little or no beneficial effect from these agents. A report of a favorable therapeutic response in a case of coccidioidomycosis given a total dose of 1.95 gm. of stilbamidine [158] led to a further trial in seven patients with proved disseminated coccidioidomycosis.[159] The stilbamidine derivative, 2-hydroxystilbamidine, because of its low toxicity, was used in total doses of from 8 to 23 gm. No cures were achieved, though some suppression of the infections was noted in five patients.

Sex hormones thus far studied have shown diethylstilbestrol and some other estrogens to be fungistatic against several pathogenic fungi, including C. immitis.[45] The in vitro fungistatic activity of diethylstilbestrol on C. immitis has been reported as excellent,[160] with moderate inhibition by testosterone, methyltestosterone, and testosterone propionate.[22] The later drug showed no protective effect in experimentally infected mice. The sulfonamides have only a slight fungistatic effect in vitro on the coccidioides organism,[161] and with triple sulfonamides combined with methyltestosterone no synergistic action was noted.[22] Two unsuccessful trials with diethylstilbestrol in the treatment of coccidioidal infections in man are reported,[162] but one case of disseminated coccidioidomycosis responded to a combination of methyltestosterone with sulfonamides [22] and another treated with testosterone cyclopentopropionate, ethinyl estradiol, and trypsin showed a complete remission.[163]

Particular mention should be made of other various compounds tested against C. immitis. A large group of antihistaminic compounds of low toxicity have shown considerable in vitro inhibition against the fungus.[56,164] Of the vanillic esters, the isobutyl derivative was the most inhibitory, while ethyl vanillate was the least inhibitory and relatively ineffective in in vitro tests.[154] A case of disseminated coccidioidomycosis treated with ethyl vanillate did not respond to therapy.[165] Rimocidin,[154,155] sodium caprylate, fradicin, and thiolutin [166] and various alkyl amines [167] also have been shown to inhibit C. immitis in vitro. Iodides, thymol, arsphenamine, methylrosaniline chloride (crystal violet, gentian violet), colloidal copper, antimony compounds, and potassium tartrate have all been tried in the treatment of the disease in man without success.[123] A case of disseminated coccidioidomycosis has been treated with protoanemonin,[168] an antibiotic which possesses in vitro activity against C. immitis, without a favorable response.

The purple dye, prodigiosin, has been found to be inhibitory in vitro to C. immitis as well as effective in animal infections. When prodigiosin was used in the treatment of 14 patients with disseminated coccidioidomycosis, apparent recovery was evident in only three.[169] Sulfonamides, penicillin, streptomycin, oxytetracycline, chlortetracycline, and aminosalicylic acid have not shown inhibitory effect on coccidioidal isolates in vitro or curative effect in vivo. Streptothricin effectively inhibits the growth of C. immitis,[170] while streptomycin enhances it.[48] Isoniazid and iproniazid have been shown in vitro not to inhibit C. immitis,[154,171] nor will these drugs modify the experimental infection in mice.[172] Thiazolsulfone (Promizole) has been considered therapeutically active in doses of 12 to 20 gm. daily in the treatment of coccidioidomycosis,[173,174] while cycloheximide has been used without effect in several patients.[175] Cortisone has been shown to have no therapeutic value in the treatment of experimental coccidioidomycosis in the mouse[176] and caused actual enhancement of the infection in the rat.[177]

Vaccine therapy with coccidioidin has been suggested as a desensitization procedure in those patients demonstrating hypersensitivity by the skin test.[123,178] Immune serum globulin from persons recovered from coccidioidal infections with high titers of complement-fixing antibodies might be helpful.[174] X-ray therapy might also benefit the localized infection.

Surgical resection of the troublesome residual pulmonary lesion (5% incidence) of coccidioidomycosis has gained increasing support as a therapeutic measure to the point where one author thinks of pulmonary coccidioidomycosis as a surgical disease.[179] However, a somewhat more conservative policy has been voiced by thoracic surgeons in a general inquiry made in 1950.[180] Only chronic cavitation with its complications necessitates surgical intervention. These include (*a*) persistent cavitation with continuing or severe hemoptysis; (*b*) rupture of a cavity with spontaneous pneumothorax, empyema, or nonexpansile lung; (*c*) giant, blocked, infected, or expanding cavity; (*d*) solid tumor, coin lesion, or coccidioidoma, and (*e*) failure of medical treatment.[181,182] Some authors feel that indications for surgery fall much shorter than those listed.[183-186] In certain series of pulmonary coccidioidomycosis treated unhesitatingly by surgical means the curative rate was high,[72,181,187] while other series reveal a high incidence of postoperative complications, such as bronchopleural fistulae, pleural disease, and recurrent cavitation.[188-190] Pneumonectomy, lobectomy, segmental resection, wedge resection, and decortication have become useful surgical procedures for residual pulmonary lesions.

In addition to resection, Winn has successfully treated cavitary coccidioidomycosis with collapse therapy by pneumothorax or pneumoperitoneum when the cavities were between 2 and 4 cm. in diameter, thin-walled, and in suitable locations.[185] Cavities less than 2 cm. tend to close spontaneously. Indications for surgical therapy in coccidioidomycosis should be clear-cut and carefully judged, for it is rare that dissemination in cavitating infections occurs,[191-194] although reactivation has been reported.[195] Most pulmonary lesions will remain benign for many years without causing difficulty to the patient.[185,196] Dissemination in coccidioidomycosis infections occurs during the acute illness.

Summary.—Of the many chemotherapeutic agents tested to date, amphotericin B given intravenously is the most promising as treatment in the threatened or proven disseminated coccidioidomycosis. Surgical resection of the residual pulmonary lesion combined with effective chemotherapy is the procedure of choice in treating the chronic manifestations of the disease. Supportive measures are still highly important in treating the primary infection, preventing dissemination, and stabilizing the chronic lesion.

Actinomycosis

Actinomycosis is a chronic suppurative mycotic disease characterized by abscesses draining through multiple sinus tracts. The infection spreads by contiguous invasion of neighboring tissues. The fungus, Actinomyces bovis, causes the majority of the infections in man. As distinctive cultural features, the organism will not grow at room temperature and requires both special media and anaerobic conditions. The endogenous source is the mouth, the organism being present about carious teeth, the gums, and tonsillar crypts. The diagnostically characteristic "sulfur granules" are microscopic filamentous growths found in the pus of actinomycotic lesions. Clinically the disease can be classified as cervicofacial, thoracic, and abdominal. The cervicofacial form comprises over half of the cases and is more amenable to treatment. By aspiration or ingestion of Actinomyces-infected materials from the mouth, the disease can spread into the thoracic or abdominal organs, and further contiguous extension may result in a wide variety of lesions.

Since 1943, penicillin has been widely used in the treatment of actinomycosis. Early failure with penicillin therapy was due to inadequate dosage and ineffective administration,[197] although in vitro sensitivity of Actinomyces to penicillin had been noted.[139, 198] More encouraging results were reported when penicillin was employed in adequate dosage.[199-211] Nichols and Herrell treated 46 patients with penicillin and followed them for periods of one to five years.[212] They found that all cultured strains of A. bovis were inhibited in vitro by 0.01 to 0.1 units of penicillin per cubic centimeter of culture medium. The effectiveness of penicillin therapy varied with the location and chronicity of the lesion and with the general physical status of the patient. On daily doses between 80,000 and 1,000,000 units given for two to seven weeks, cervicofacial actinomycosis responded favorably in 90% of the cases. More spectacular was the recovery in 56% of the pulmonary cases and 82% of the more serious abdominal and pelvic cases of actinomycosis. In mild cases of actinomycosis recovery has been shown to occur without benefit of treatment.

Since the nature of the tissue reaction in actinomycosis is such that a satisfactory level of penicillin or other therapeutic agent in the infected tissue is difficult to attain, a more intensive and prolonged period of therapy is indicated.[213-216] In recent years from 1,000,000 to 6,000,000 units of penicillin has been given daily for three to six months to prevent relapse.[217,218] Even this dosage schedule has proved inadequate at times, and the use of larger daily doses of penicillin is warranted. Harvey et al.[214] recently advocated the use of 10,000,000 to 20,000,000 units of penicillin, given daily by infusion over a 12-hour period for 30 to 45 days. When indicated, surgical excision and drainage of infected tissues should then be performed. After surgery, 2,000,000 to 5,000,000 units of penicillin has been given intramuscularly or 5,000,000 units orally daily for an additional 12 to 18 months. In this study of 37 patients, only 14% treated before the penicillin era were cured. This was in contrast to 77% who responded favorably to penicillin therapy alone or in combination with surgical procedures.

Several in vitro studies have shown that erythromycin, chloramphenicol, streptomycin, chlortetracycline, oxytetracycline, tetracycline, bacitracin, neomycin, carbomycin, and nitrofurantoin are active drugs against A. bovis.[219-225] This organism, however, resisted the action of cycloheximide, potassium iodide, and the antituberculous agents other than dihydrostreptomycin. Cures in human actinomycosis have been reported with the use of chlortetracycline,[226-231] oxytetracycline,[216,232] tetracycline,[233,234] chloramphenicol,[229,235] streptomycin,[236-239] and erythromycin.[240] In spite of lack of sensitivity of A. bovis in vitro to stilbamidine and isoniazid, a cure with stilbamidine[241] and several cures with isoniazid[242, 243] have been reported.

Since strains of Actinomyces may show variations in their susceptibility to the same chemotherapeutic agents, in vitro sensitivity of the isolated organism should be determined whenever possible. The best single or combined therapy could thus be instituted to insure against relapse. The broad-spectrum antibiotics have a limited usefulness in the treatment of actinomycosis because of toxic effects from long-term administration and the slow development of resistance of the organism to them over a relatively short time of 16 weeks or less. On the other hand, the Actinomyces organism is extremely sensitive to the action of penicillin, erythromycin, and carbomycin and does not develop resistance to these antibiotics over long periods of treatment.[244]

Since 1938, the sulfonamides—sulfadiazine and sulfathiazole[204,245-250]—and sulfoxone (Diasone)[251] have been employed successfully in the treatment of actinomycosis. Adjunct therapy has usually consisted of treatment with potassium iodide and surgical incision and drainage. Sulfonamide blood levels from 10 to 15 mg. per 100 ml. or more should be maintained during the period of therapy, extending from four to six months. Generally, the sulfonamides are much less effective against Actinomyces in vitro than penicillin or the broad-spectrum antibiotics.[220,225] Strain variations in sensitivity tests with the sulfonamides and sulfones have also been noted.[252,253]

Potassium iodide is still advocated as a supplementary treatment to the antibiotics but never as the only treatment.[60] It is believed that iodine therapy results in resorption of fibrous tissue in the actinomycotic lesion, allowing the antibiotics to gain access to the causative organism. Thymol, copper sulfate, vaccine therapy, and other agents have been used in the past without any proved worth except in the cervicofacial form of the disease. Roentgen therapy has been advocated in the treatment of cervicofacial actinomycosis.

As in the treatment of nocardiosis, combined surgical drainage and excision along with antibiotics or sulfonamide therapy offer the best therapy for recovery.[216,254] Pulmonary resection has been performed in a few instances when other forms of therapy have failed.[255]

Summary.—Large daily doses of penicillin (6,000,000 to 12,000,000 units) combined with surgical drainage of sinus tract and abscesses has been the most successful therapeutic program in the treatment of actinomycosis. Antibiotic therapy should be continued for several months. The sulfonamides and broad-spectrum antibiotics have also been employed alone and in combination with penicillin or surgical intervention in the successful treatment of actinomycosis.

Nocardiosis

Nocardiosis is a fungus infection which closely simulates actinomycosis. The Nocardia asteroides organism has a world-wide geographic distribution, with soil being its natural habitat. It is a bacteria-like fungus, occurring in infected tissues or materials as filamentous rods which may segment into short bacillary or even coccal forms. The Gram-positive rod-like filaments may be acid-fast and grow with ease aerobically, as opposed to A. bovis, which requires an anaerobic environment.

In a very recent review of the 95 cases of nocardiosis reported in the world literature, over two-thirds had pulmonary involvement, indicating that the usual portal of entry is the respiratory tract.[256] The gastrointestinal tract and superficial wounds can also serve as portals of entry. Spread from the pulmonary focus tends to be hematogenous, so that any organ or tissue, particularly the brain and subcutaneous tissues, may be subsequently involved. Nocardiosis can mimic actinomycosis, with the development of sinus tracts by contiguous spread and yellow granules in the exudate.

After sulfonamide therapy proved effective in actinomycosis, it was also tried with success in treating nocardiosis as early as 1944.[250] In these early treated cases the sulfonamides were used in conjunction with x-ray therapy, surgical drainage, and potas-

sium iodide. Sulfadiazine and sulfathiazole were found to suppress aerobic growth of Nocardia,[252] and the importance of sulfadiazine added to any therapeutic regimen in this disease was soon forcefully demonstrated clinically.[218,256-267] Thomas and Pulaski gave 8.0 gm. of sulfadiazine per day in divided doses for a four-and-one-half-month period (total 1168 gm.), with complete recovery of a suppurative pulmonary nocardiosis with hematogenous spread to the leg. It is a remarkable fact that there was no improvement in this patient with use of tetracycline or erythromycin except when sulfadiazine was instituted, even though the organism was sensitive, in vitro, to erythromycin but not to penicillin, streptomycin, tetracycline, and chloramphenicol. Prolonged high doses of sulfadiazine, with a total of 1268 gm. being given over a five-month period, were also stressed by Glover et al. The maintenance of blood levels of sulfonamide of 10 to 20 mg. per 100 ml. is essential for effective therapy. This requires a dosage of 1 to 2 gm. given every four hours, which should be continued for six months or longer in the chronic infections.[60]

Sulfadiazine is the drug of choice in the treatment of nocardiosis. However, in vitro sensitivity of the Nocardia fungus does not parallel in vivo findings with the sulfanilamides and antibiotics. Sulfadiazine has been shown to be relatively ineffective in vitro, particularly when compared with chlortetracycline, chloramphenicol, oxytetracycline, and streptomycin. Yet in vivo tests in mice revealed that sulfadiazine gave almost complete protection, while the broad-spectrum antibiotics only prolonged the survival time.[220,268,269] It has been conjectured from these results that fungistatic action at concentrations below complete inhibition of growth only is needed to allow the natural defenses of the host to overcome the infection. In in vitro studies, sulfamerazine was found to be somewhat more effective than sulfadiazine, sulfathiazole, sulfisoxazole, and sulfamethazine in controlling the growth of most Nocardia strains tested, while the sulfones, sulfoxone and thiazolsulfone, were even more effective than the sulfonamides against N. asteroides.[269] A clinical case successfully treated with sulfoxone has been reported.[270]

Apparent cures of nocardiosis have been reported in which the disease was treated principally with penicillin combined with streptomycin or other broad-spectrum antibiotics.[271-277] Resistance to streptomycin and penicillin in vitro has been shown to develop.[278] Penicillin,[204] as well as pregnenolone acetate[279] has been shown to exert a therapeutic effect in the treatment of nocardiosis. Cycloheximide was not effective in a therapeutic trial.[280] Nocardiosis has not responded to a number of other therapeutic agents.[281]

Stilbamidine and 2-hydroxystilbamidine inhibit the growth of N. asteroides, and so these drugs in appropriate doses would be expected to be effective in the treatment of Nocardia infections in man.[218] Amphotericin B, though very promising as therapy in the other deep-seated mycoses, is completely ineffective against the Nocardia species by in vitro testing.[2,5]

In Ballenger and Goldring's careful review of nocardiosis cases[256] it is pointed out that the mortality rate was 68.4%, with 50% of the fatal cases having received no therapy. However, the great majority of treated cases have recovered when the sulfonamides have been used singly or in combination with other antibiotics and surgical intervention. Inadequate dosages given belatedly and for too brief a period accounts for most treatment failures. Therapy must continue several months to years after symptoms and findings clear to prevent recurrences. The vigorous therapy suggested by Peabody and Seabury[218] consists of initial treatment with 4 gm. to as high as 12 gm. of sulfadiazine per day along with 2 gm. of streptomycin or another broad-spectrum antibiotic. Later the therapy is modified according to sensitivity tests if there is no response.

Surgical intervention with adequate drainage or extensive excision of an infected area often must augment the supportive and

chemotherapeutic treatment of nocardiosis. Incision and drainage removes toxic infectious materials and favors wound healing. Lobectomy and pneumonectomy have been used in selected cases which were resistant to other forms of therapy. Resection of a pulmonary lesion with recovery has been reported, although the diagnosis of nocardiosis was arrived at after surgery.[271] It is most important to combine sulfadiazine therapy with surgical intervention, although chemotherapy, in turn, has not modified the principle of surgical drainage. Iodides, thymol, and roentgen therapy are still considered by some to have a role in treatment of nocardiosis, but only in conjunction with the more superior treatment existing today.[250]

Summary.—The sulfonamides are the drugs of choice in the treatment of nocardiosis but should be combined with an effective broad-spectrum antibiotic because of the seriousness of the infection. Sulfonamide blood levels of 10 to 20 mg. per 100 ml. should be maintained over a period of several months. Sulfadiazine has been extensively employed, but sulfamerazine appears to be equally effective. Surgical intervention with adequate drainage or excision of lesions along with appropriate chemotherapy offers the most promising results in nocardiosis.

Cryptococcosis

Cryptococcosis, or torulosis, is a serious fungal disease caused by the organism, Cryptococcus neoformans. As a saprophyte with world-wide distribution, it has been isolated in nature only from fruit, raw milk, soil, and pigeon droppings. Uniquely, this fungus does not possess a mycelial phase. It grows solely as a thickly encapsulated yeast-like organism both in tissue and in culture on common fungal media. The portal of entry is primarily the respiratory tract. The yeast is inhaled when air-borne from its reservoir in the soil. The alimentary tract, the skin, and the mucous membranes may also serve as localized sites for inoculation. Since C. neoformans has a high predilection for the central nervous system, it is the chief cause of mycotic meningoencephalitis in man. The primary pulmonary lesions may remain so insignificant roentgenologically or clinically that the disease is often first recognized only when symptoms of central nervous system involvement appear. The dissemination from the lungs to other parts of the body is by hematogenous spread. A few meningoencephalitic cases have demonstrated periods of remission or have been able to live in balance with their infection for relatively long periods of time.

The treatment of cryptococcosis is far from being satisfactory, for specific therapeutic agents are not yet available. Littman and Zimmerman [282] have recently provided a most exacting account of the status of treatment of cryptococcal infections.

Since hematogenous spread to the nervous system makes the prognosis in cryptococcosis extremely poor, early surgical excision of the local primary pulmonary lesion offers one of the most encouraging methods of treatment. A cure results only if the infected lung tissue is resected before dissemination to other tissues occurs. Thus, an early diagnosis is imperative. Surgical resection of a circumscribed pulmonary lesion was advocated first in 1937, by Taber,[283] and the value of this procedure has been repeatedly demonstrated since that time.[284-294] A lobectomy or pneumonectomy is recommended to avoid any spread that might follow removal of small segments of infected lung tissue. As soon as a diagnosis of pulmonary cryptococcosis is made, it is advisable to remove the lesion immediately and not wait for a possible spontaneous regression, which sometimes occurs. Once spread of the infection has occurred to bone, joints, eye, brain, or skin and has become localized, surgical excision should also be undertaken.[295-299]

The most promising current treatment of cryptococcosis rests in the new antifungal antibiotic, amphotericin B. It has a significant in vitro effectiveness against the Cryptococcus fungus,[1,2,4,5] and in vivo tests on

mice experimentally infected with this fungus have shown the drug to be highly effective in prolonging the survival time when administered orally or intraperitoneally.[3,7] The drug has resulted in clinical arrest of a case of cryptococcal meningitis in a diabetic.[300] The isolated organism was demonstrated to have complete insensitivity to all the common antibiotics but pronounced sensitivity to amphotericin B. There was no response to oral amphotericin medication, but good clinical improvement resulted when intravenous doses of 100 mg. were administered daily and later every other day for five weeks. Although spontaneous remissions in cryptococcosis are known to occur, the arrest of the disease in the above case seemed to be the result of treatment with amphotericin B. An increasing number of cases of systemic cryptococcosis have shown clinical improvement following treatment with intravenous amphotericin B.[6,9,10] However, follow-up of these cases has not been sufficiently long to evaluate the lasting effect of this therapy. Failures in treatment of cryptococcosis with amphotericin B have also been noted, and so this antibiotic can not be considered the specific therapy so badly needed for this mycotic disease.[5,6,9,10] The intrathecal administration of amphotericin B in the amount of 0.5 to 1.0 mg. in 5 ml. of water has been used successfully in a few cases of severe cryptococcal meningitis.

Encouraging results have also been reported with 2-hydroxystilbamidine in the treatment of generalized cryptococcal infections.[301,302] The total amounts given were 4.05 gm. and 10.04 gm. intravenously, respectively, to the two cases reported. Stilbamidine has not been successful, as reported in four cases of cryptococcal meningitis.[303,304] Propamidine and 2-hydroxystilbamidine are the most active diamidines against the cryptococcus organism in in vitro tests.[85,302,305] Animal studies, however, have not demonstrated the diamidines to be protective in Cryptococcus-infected mice.[305-307]

None of the usual antibiotic agents have been found to be worthwhile in the treatment of cryptococcosis, although cycloheximide and nystatin deserve brief mention. Cycloheximide is known to have marked fungicidal properties in vitro for C. neoformans, the only pathogenic fungus sensitive to the drug.[34,40] However, this antibiotic was ineffective in treatment of experimental infections.[308] Cycloheximide has received a very significant therapeutic trial in the treatment of cryptococcosis in man. Only two clinical remissions have been reported,[309,310] although in general it has been discouragingly ineffective, even reportedly hastening a patient's death when used in a recent trial.[311]

In in vitro tests nystatin has prevented the growth of C. neoformans in culture,[40] and the parenteral use of this antibiotic has prolonged the life and effected some cures in experimentally infected animals.[34] The excellent therapeutic results with nystatin in mice infected with the Cryptococcus organism have been well documented by Campbell et al.[151] However, a few infections in man have been treated with nystatin to date without beneficial results.[282]

Ethyl vanillate has been shown to be ineffective in the treatment of cryptococcosis in one therapeutic trial.[312] Beta-diethylaminoethyl fencholate (MRD-112) [4,23] candicidin, anisomycin,[4] and Nepera 1968 [4,313] have shown an effective antifungal activity against C. neoformans in vitro. Only β-diethylaminoethyl fencholate has been evaluated in clinical trials on cryptococcal meningitis and proved ineffective.[6] C. neoformans was the most sensitive of the pathogenic fungi tested with filipin [314] and was completely inhibited by eulicin [53] in low concentration in vitro.

Successful results with sulfadiazine and other sulfonamides have been reported in only a few instances.[123,315,316] As the Cryptococcus organism is quite resistant to the sulfonamides in vitro, large doses are recommended in treatment of cryptococcosis, so that blood levels of 8 to 14 mg. per 100 ml. or higher are maintained.[317,318] But even such doses still fall far short of that found necessary to inhibit the organism in vitro.[253]

When the sulfonamides are employed, treatment should continue for some months after the disappearance of symptoms.

The Cryptococcus organism has shown enhancement of growth in media containing steroids.[45] Shortening of the survival time in mice infected with this fungal organism occurred when they were treated with cortisone or estradiol.[319,320] Testosterone, methyltestosterone, and testosterone propionate have no significant antifungal effect against C. neoformans.[22]

With such limited value seemingly attached to chemotherapeutic agents, the usual supportive measures become extremely important. A recent review of all the reported cases of cryptococcosis with cutaneous manifestations emphasizes well that when systemic involvement has occurred therapy is of little avail.[321] Radiation therapy to the localized lesions has been recommended and combined with surgical procedures. Iodides have not been singularly effective, though they too have frequently been used in combination with other forms of therapy.[322-324] Fever therapy has fallen into some disrepute, and the administration of autogenous vaccine has not altered the course of cryptococcosis in man.

Summary.—Early and wide surgical removal of pulmonary lesions due to C. neoformans is of major importance in preventing a generalized spread of the infections and meningitis in particular. The new antibiotic, amphotericin B, given intravenously and intrathecally in adequate dosage over a long period of time is the most effective agent available for the treatment of cryptococcosis. It seems appropriate to combine this antibiotic with surgical resections and drainage of lesions. In a few cases sulfadiazine and 2-hydroxystilbamidine have been employed successfully in the treatment of cryptococcosis. Cortisone and other steroids are of no clinical value and even hazardous in the treatment of cryptococcosis.

Moniliasis

Moniliasis is an acute or subacute infection caused by species of Candida. The commonest strain is Candida albicans, a fungal organism existing normally as a saprophyte on the skin, in the mouth, and in the intestinal tract of man. Thus, the origin is endogenous and the fungus is recognized throughout the world. Candida grows in typical creamy yeast-like colonies when cultured on special glucose media. On nutritionally poor media, such as corn-meal agar, it produces a mycelial growth bearing many blastospores with distinctive thick-walled terminal chlamydospores. C. albicans causes localized infections of the skin, mucous membranes, bronchopulmonary system, and occasionally disseminated illnesses. Predisposing factors in Candida infections are primary debilitating diseases, diabetes mellitus, pregnancy, obesity, lung cancer, and tuberculosis. The first line of attack in treatment of a Candida infection is to treat the underlying disease, which is frequently associated with poor nutrition.

In recent years it has been clearly documented that intensive use of broad-spectrum-antibiotic, steroid, and irradiation therapies may be followed by serious mycotic infections due to C. albicans.[325-332] Cortisone and roentgen radiation have been shown to shorten the survival time of mice infected with C. albicans and to increase the severity of such infections.[319,329,333-335] Estradiol has also been shown to shorten the survival time in experimental moniliasis and to act synergistically with cortisone.[319] Thus, when patients have illnesses which require steroid therapy, careful daily observations for the detection of superimposed C. albicans infections must be made.

Nystatin has been established by in vitro tests [34,40,336-339] and experimental infections in mice and rabbits [152,337,340-344] to be highly effective against the fungus, C. albicans. It is now considered the drug of choice in the treatment of Candida infections in man. A total of 54 different strains of C. albicans has been shown to have essentially the same high sensitivity to nystatin; 74% of these strains were susceptible to 8 units or less of nystatin per milliliter.[345] The development of resistance of strains of C. albicans

to nystatin has not been observed in experimental studies.[35]

All clinical forms of moniliasis have been successfully treated with nystatin thus far. Oral moniliasis in infants and young children has been quickly brought under control by the local and oral use of nystatin usually administered over 3- to 15-day periods.[338, 346-349] Cutaneous moniliasis has responded best to combined topical and oral nystatin.[337, 348-356] The earlier treatment is begun the greater is the response to nystatin therapy. Failures in treatment of moniliasis with nystatin are the long-standing infections. Cure rates in different series of cutaneous moniliasis studied have ranged from 75% to 95%.[350-353,356] Even the generalized infections of the skin have been easily managed by oral nystatin.[350,357] Abdominal ulcerations caused particularly around colostomies have been cured with oral and local nystatin.[358] Monilial vulvovaginitis has responded most successfully to nystatin in suppository, tablet, or ointment form.[347, 348,359-363]

The pulmonary and disseminated forms of moniliasis have been treated satisfactorily with nystatin but not with such convincing results as in the case of skin infections. One reported case of pulmonary moniliasis treated with nystatin cleared roentgenographically, but the sputum remained positive for C. albicans by culture.[364] The systemic manifestations of moniliasis in another patient subsided completely following nystatin therapy.[357] A Candida pneumonia associated with thrush in an infant was probably cured by oral nystatin.[365] A few systemic cases have been resistant to nystatin.[60,366] Thirteen cases of generalized moniliasis were reportedly cured.[337] The excessive numbers of Candida organisms in the gastrointestinal tract which might lead to systemic spread or relapse during the use of broad-spectrum antibiotics have been effectively kept in check by nystatin.[337,342,367] A recent report on treatment of intestinal moniliasis in adults showed that nystatin only gave temporary improvement, while methylrosaniline chloride produced a few cures.[368] Oral nystatin should be combined with practically all forms of local administration of the drug, since the gastrointestinal tract is most frequently the reservoir of Candida. The poor absorption of this agent from the gastrointestinal tract really limits its usefulness in pulmonary and systemic forms of the disease.

The newer antifungal antibiotic, amphotericin B, also shows great promise as an effective agent for the treatment of moniliasis. It has proved highly inhibitory to the Candida species in vitro[2] and by tissue-culture tests.[4] No strains of C. albicans have been found to be resistant to the drug.[9] Treatment by the intraperitoneal or oral routes with amphotericin B of mice infected with C. albicans successfully cured the infection if given early and prolonged survival time greatly if given late in the disease.[1,5,7] The drug has been shown to eliminate C. albicans from the fecal flora when given orally to man.[9,369] In cutaneous moniliasis, nystatin has proved slightly superior to amphotericin B in one comparative series.[353] When used in ointment forms, amphotericin B brought about a cure in 80% of 75 infants and young children treated for 8 to 13 days.

Candida septicemia, or systemic Candida infections, treated with oral amphotericin B has responded minimally as would be expected because of poor absorption of the drug. On the other hand, intravenous therapy has been dramatically effective in actually clearing the blood stream of the Candida organism within a few days.[10] Cases of pulmonary moniliasis reported have also been successfully treated with oral dosages,[9] but a more impressive response can be expected from intravenous or intramuscular administration. Though no benefit is gained from parenteral administration of amphotericin B in treating the cutaneous, mucocutaneous, and gastrointestinal Candida infections, this route is extremely effective in preventing or treating the disseminated illnesses.

Up to the advent of nystatin, the most accepted therapy for moniliasis was

methylrosaniline chloride, and it proved quite universally useful when it could be applied topically.[123] Intravenous doses of 5 mg. of methylrosaniline chloride per kilogram of body weight daily for less than one week has been used in treating the pulmonary and disseminated moniliasis. Propionate vaginal jelly has given an 80% cure rate in Candida vulvovaginitis in nonpregnant women.[370] A Carbowax-sulfur ointment has been used successfully in Candida infections other than the systemic form.[371] Potassium iodide has had its advocates as treatment for this fungal infection also,[123] and ethyl iodide inhalations are still being advocated, coupled with other antifungal therapy.[372]

Comments on other chemotherapeutic agents and antibiotics of interest are indicated to complete the knowledge concerning the present status of possible therapy. Some 100 compounds and mixtures of these having fungistatic properties were tested by the disk method against Candida species.[373] These included acids, esters, alcohols, aldehydes, antibiotics, antihistaminics, detergents, dyes, halogens, heavy metals, oxidizing agents, phenols, sulfonamides, and dermatological preparations. There were only four drugs that were significantly fungistatic: sodium caprylate, boric acid, methylrosaniline chloride, and metacresylacetate (Cresatin). No effectiveness against Candida was demonstrated by streptomycin, penicillin, oxytetracycline, chlortetracycline, or sulfathiazole. However, there was occasional enhancement of growth by these agents and extreme enhancement particularly with chlortetracycline and *p*-hydroxybenzoic acid (Paraben). Esters of *p*-hydroxybenzoic acid have also been used clinically in an attempt to avoid complications in Candida infections[374] because of their inhibitory action against C. albicans.[375] Sulfanilamide, testosterone, methyltestosterone, and testosterone propionate have all proved completely ineffective against C. albicans in another study.[22]

Another new antibiotic, Nepera 1968, has been found markedly inhibitory to pathogenic fungi in vitro[376] and also effective in markedly supressing mortality in mice infected with C. albicans.[51] Candicidin completely inhibits the growth of C. albicans by the in vitro technique[4,377] but is toxic for man.

Oral undecylenic acid has been used to prevent Candida infection secondary to broad-spectrum antibiosis and in a dosage of 0.44 gm. for every 250 mg. of broad-spectrum antibiotic.[378] Stilbamidine and 2-hydroxystilbamidine have been shown to possess a moderate degree of activity against C. albicans in vitro, but in vivo tests in mice demonstrated that both agents were ineffective.[85] Relative resistance of C. albicans to in vitro action of the nitrostyrenes has been found, but favorable clinical results have been attained in local treatment of oral or vaginal moniliasis by either mouth rinse or vaginal douche, respectively.[141] Brilliant green and methylene blue aerosol inhalations have been followed by improvement of cases of bronchopulmonary moniliasis.[379-381]

Summary.—Two antifungal antibiotics stand out as the agents of choice in the treatment of mucocutaneous, pulmonary, and systemic moniliasis. These are nystatin for use orally and topically and amphotericin B for use intravenously and intramuscularly. Methylrosaniline chloride still has a place in the treatment of moniliasis.

It is evident from the literature of the last several years that the steroids are contraindicated in the treatment of C. albicans infections and occasionally foster the development of this infection in patients receiving long-term steroid therapy. Candida infections also complicate other diseases which require mechlorethamine hydrochloride for treatment. In such cases the use of the above antibiotics as prophylactics are indicated if C. albicans can be cultured from the mouth or gastrointestinal tract of patients receiving steroid or mechlorethamine hydrochloride therapy, which lowers host resistance.

Aspergillosis

Aspergillus fumigatus is the commonest strain capable of causing aspergillosis. It is ubiquitous in nature, is found most commonly in soil and decaying organic matter, and is one of the bothersome contaminants of culture plates in any laboratory. Persons exposed repeatedly to massive quantities of the organism growing in compost heaps, "spoiled" grain, straw, hay, moldy feeds, or rotting wood may be infected via the respiratory tract. Typically, the Aspergillus organism grows a conidiophore, the end of which bears a swollen vesicle from which arise long chains of conidia, or spores.

The Aspergillus fungus may be a primary or secondary invader of human tissue. Aspergillosis is found not infrequently in association with other chronic lung diseases, such as pulmonary tuberculosis, lung abscesses, cysts, bronchiectasis, chronic bronchitis, and carcinoma. Primary pulmonary aspergillosis has been frequently associated with asthma and eosinophilia. Aspergillosis may manifest itself as (*a*) acute tracheobronchitis, (*b*) bronchopneumonia or migrating pneumonitis,[4] (*c*) chronic granulomata with or without cavitation (pseudotuberculosis), and (*d*) single or multiple round densities (aspergilloma, mycetoma, or intracavitary fungus ball). Generalized Aspergillus infections are rare even in cases where there is extensive pulmonary involvement, although dissemination has followed the long-term use of antibiotics.[382] Uncontrolled diabetes mellitus may predispose to pulmonary aspergillosis. Treatment, therefore, starts first with the control of such primary underlying diseases.

The treatment of choice in localized forms of aspergillosis is surgical resection or draining of the focus of infection. Such therapy has provided many successful cures.[383-393] Pulmonary segmental resection and lobectomy have successfully removed lesions which failed to respond to other therapeutic measures.

No specific drug has been reported to be particularly effective, although iodides, arsenicals, sulfonamides, penicillin, and streptomycin have been advocated for the treatment of aspergillosis. Hetherington used x-ray treatment for six months, autogenous vaccine, and thymol-iodide without modifying the progression of a case of aspergillosis.[394] Desensitization with autogenous vaccine has been recommended if the patient is sensitive to his own organisms.[60] Iodides and thymol have been occasionally efficacious in the treatment of tracheobronchitic and tubercular forms of the disease. Hinson et al., in a review of the literature and report of eight cases of pulmonary aspergillosis, emphasized that they found no effective form of medical treatment.[387] They advised supportive measures and postural drainage to dislodge plugs from occluded bronchi. In one case of a probable Aspergillus abscess, large doses of penicillin (20,000,000 units per day) produced clinical improvement and shrinkage of the cavity[386] prior to surgical resection. Improvement following the treatment of pulmonary aspergillosis with antibiotics can be explained best by the eradication of infection due to invading bacteria.[386,395] On the basis of some case reports it may be speculated that antibiotics are not only ineffective against this fungus but may also be harmful in certain instances. Dissemination seems to have occurred in several cases reported after sulfonamides and broad-spectrum antibiotics were used.[396-398] It has been postulated that the growth of the Aspergillus fungus was enhanced by intrathecal administration of penicillin in a reported case of pneumococcal meningitis.[399]

In vitro studies to demonstrate sensitivity of the Aspergillus fungus to sulfonamides, penicillin, streptomycin, oxytetracycline, chlortetracycline, tetracycline, chloramphenicol, erythromycin, potassium iodide, and mercuric iodide red have been done.[387,400] Penicillin was inactive against A. fumigatus. All the other antibiotics and potassium iodide were fungistatic or prevented fructification.

Mercuric iodide red was markedly fungicidal.

Intravenous 2-hydroxystilbamidine, 0.15 gm. a day for two 10-day periods spaced a week apart, resulted in clinical and radiological improvement in a cavitary form of pulmonary aspergillosis.[401] Further treatment with nystatin orally, 500,000 units three times a day, following the administration of 2-hydroxystilbamidine for eight weeks, was accompanied by further clearing and almost total disappearance of the abscess cavity. Seven months after discontinuance of therapy the patient died of renal failure. Inhalation of nystatin in suspension or of solutions of brilliant green or 2-hydroxystilbamidine has been reported as being effective in suppressing or eradicating A. fumigatus from bronchial secretions.[402] Isoniazid has been used in the treatment of the aspergilloma or fungal ball,[402] although it is unlikely that the drug affected the in vivo growth of the fungus. In vitro tests reveal that isoniazid will inhibit fructification but not mycelial growth.

Amphotericin B has no significant in vitro activity against Aspergillus species, although amphotericin A has some.[1,2] Oral treatment with amphotericin A of a case with an Aspergillus granuloma of the left orbital region did not produce favorable response.[9] Eulicin as a new antibiotic has shown marked antifungal effect in vitro against Aspergillus niger.[403]

Both cortisone and corticotropin have been shown to shorten significantly the survival time in mice infected with Aspergillus fungus.[319]

Summary.—At the present time there is no effective drug or antibiotic for the treatment of Aspergillus fungus infections. Nystatin and 2-hydroxystilbamidine need further evaluation. The use of these agents along with surgical excision and drainage of lesions appears to be the most rational therapeutic approach. Careful attention to underlying diseases, such as diabetes mellitus, is important. The steroids are contraindicated in the treatment of any form of aspergillosis.

Sporotrichosis

Sporotrichosis is a chronic mycotic infection clinically classified according to the location of the lesions as lymphatic, epidermal, mucosal, skeletal, and visceral types. The fungal agent pathogenic to man is Sporotrichum schenckii, which grows saprophytically in the soil or on plants and wood. It is biphasic; the mycelial phase in nature produces conidiophores terminating in clusters of pyriform conidia, and the yeast or parasitic phase grows as round to fusiform budding cells. The disease has a world-wide distribution. The primary infection occurs most frequently from the introduction of the organism into small cutaneous or mucosal wounds or abrasions, although such a contact with the organism is frequently lacking in systemic forms. The nodular skin lesion thus produced advances to a chancre, and numerous secondary subcutaneous nodules form along the draining lymphatics. Dissemination with or without pulmonary involvement may occur, though rather rarely, and hematogenous spread may involve many organs and produce multiple subcutaneous nodules and ulcerations.

Until recently, iodides have been considered specific in the treatment of sporotrichosis. Iodides will not prevent experimental infections in the rat, but they will cure the infected animal.[404] It is surprising that the organism also grows well in culture media containing 10% concentration of potassium iodide. In spite of these observations, it is well documented that the localized lymphatic from of the disease will respond favorably to iodides within weeks to a few months.[123, 405-412] Treatment consists of a saturated solution of potassium iodide given orally in increasing individual doses up to a total of 40 drops t. i. d. or sodium iodide intravenously in daily doses of 1 gm. Clinical response will not be immediate, and iodide therapy should be continued for a least four weeks after apparent cure is attained.[413] Skin ulcers may be treated locally with an aqueous solution containing 2% potassium iodide and 0.2% iodine [123] or perchloride of

mercury followed by glycerin and 10% ichthammol (Ichthyol) dressings.[410] Healing of an isolated lesion has been shown to follow irradiation therapy.[414] Desensitization of the hypersensitive patient has also been recommended with autogenous vaccine.[123] Surgical incision of local lesions should be avoided to prevent further suppuration and ulceration, but excisional therapy might be indicated. Cultures should be done by needle aspiration.

The response to iodide therapy in systemic sporotrichal involvement may frequently be unsuccessful.[415] Consequently, other therapeutic agents need to be evaluated. Recently, the aromatic diamidines have been tried in the treatment of sporotrichosis with promising results. Stilbamidine, Pentamidine, and propamidine have all demonstrated in vitro effectiveness against S. schenckii.[83 160] The successful treatment of a case of lymphatic sporotrichosis was achieved with a total dose of 0.9 gm. of stilbamidine given in 150 mg. doses intravenously three times weekly for two weeks.[416] The response to therapy was judged to be more rapid than if iodides had been used.

Since 2-hydroxystilbamidine is considered a drug of much lower toxicity, it has been used in the treatment of systemic sporotrichosis with central nervous system involvement.[415] The daily dose was 200 to 250 mg. intravenously for one month and resulted in a definite clinical and neurological improvement. Subcutaneous nodules disappeared after two weeks of therapy. Severe allergic sensitivity prevented continuing therapy with 2-hydroxystilbamidine, and the patient eventually succumbed to the infection. The diamidines have appeared of sufficient curative value in other cases of systemic sporotrichosis to warrant further evaluation.[412] However, in the only other recently reported case of leptomeningitis caused by S. schenckii failure of therapy with potassium iodide, 2-hydroxystilbamidine, typhoid vaccine, penicillin, streptomycin, and chloramphenicol singly or in combination occurred.[417]

S. schenckii appears to have a high in vitro sensitivity to amphotericin B,[1,2,4] although no sensitivity was noted by Halde et al.[5] Clinical trials with amphotericin B have not yet been reported, except for treatment of a Sporotrichum synovitis of a knee which did not respond to the oral form of the antibiotic.[9]

An in vitro effect of nystatin against S. schenckii has been demonstrated.[34] Nystatin has also been observed to effect favorably the course of sporotrichosis in experimentally infected mice.[151] Three times the amount of the antibiotic was necessary compared to that required for treating moniliasis, histoplasmosis, coccidioidomycosis, and cryptococcosis in experimentally infected mice. Nystatin therapy was favorable when given both at the onset and after infection was established.

The antibiotic, Nepera 1968, has a marked in vitro action against S. schenckii and has prolonged the survival time of mice with experimental sporotrichosis.[51]

Summary.—At the present time iodide therapy appears to be the treatment of choice. The newer antifungal antibiotics, nystatin, amphotericin B, and Nepera 1968 need further clinical evaluation.

Geotrichosis

Geotrichosis as a fungal disease entity has been relatively unimportant to date, although many cases have probably gone undiagnosed. The causative organisms, Geotrichum candidum and related species, are found as saprophytes in soil or decaying organic matter and probably have a worldwide distribution. They are also found commonly in the mouth, bronchi, and intestinal tract. Rectangular arthrospores of G. candidum resemble and may be mistaken for Coccidioides immitis. When the Geotrichum fungus is found in a lesion it is difficult to determine whether it represents a primary or secondary invader. From a paucity of reports the clinical types of geotrichosis may be classified as oral, intestinal, and bronchopulmonary, the latter simulating chronic

bacterial bronchitis or pulmonary tuberculosis. The lesions of the mucous membranes resemble the "thrush-like" growths of Candida. Thin-walled cavities in the lung parenchyma of a case of geotrichosis have been confused with infections due to Coccidioides immitis. Reports of Geotrichum septicemia emphasize the need for greater awareness of this agent as a cause of disease.[418,419]

The bronchopulmonary lesions due to Geotrichum have responded well to sodium iodide intravenously or potassium iodide orally. Doses of 1 gm. of sodium iodide intravenously and/or daily increasing doses of oral potassium iodide (20 to 30 drops t. i. d. maximum) have produced cures.[411, 420-424] Such therapy must be continued until the lesions have healed.

Roentgen irradiation combined with iodide therapy has been helpful in certain cases.[422] Heat-killed autogenous vaccines have been employed in an attempt to desensitize the patient.

In vitro study has shown that Geotrichum organisms are sensitive to neomycin but resistant to penicillin, streptomycin, chlortetracycline, and chloramphenicol.[425] Neomycin has been effective in the treatment of Geotrichum septicemia in a 79-year-old diabetic man after penicillin, chloramphenicol, and chlortetracycline failed singly and in combination.[418]

The recommended therapy for the oral manifestations of geotrichosis is a 1:10,000 solution of methylrosaniline chloride in 10% alcohol or a gargle of 1:100,000 solution of methylrosaniline chloride. Phenyl salicylate-coated capsules of methylrosaniline chloride for the intestinal infection are given in doses of 32 mg. three times a day.[411]

Amphotericin B has no significant in vitro activity against Geotrichum, but amphotericin A has some.[1,2] However, distinct clinical improvement has been reported in a case of pulmonary geotrichosis treated with oral amphotericin B and nystatin in aerosol form.[9]

Summary.—Infections due to Geotrichum organisms are probably more prevalent than are now being recognized. At present, treatment with iodides, methylrosaniline chloride, and neomycin have been the most successful, but nystatin and amphotericin B need further evaluation.

Mucormycosis

Mucormycosis is being described as a "new disease" in the United States[426] and is caused by fungi of the Mucor, Rhizopus, and Absidia genera. It is a widely distributed organisms that grows rapidly and abundantly on culture, frequently as a frank contaminant. The hyphae are broad and nonseptate, bearing sporangia containing many small spores. The infection is acute, rather than chronic, with an affinity for blood vessels and lymphatics, resulting in thrombosis and infection. The respiratory tract is the chief portal of entry, the common forms of the disease being ocular, cerebral, pulmonary, intestinal, and disseminated. Mucormycosis is most frequently found in association with diabetes mellitus, leukemia, and multiple myeloma. Diabetic coma and acidosis are strikingly common to cases of mucormycosis. Diagnosis must be based on demonstration of the organisms in a lesion and not by cultures only, since contamination is so frequent. Of the 10 proved cases of pulmonary mucormycosis reported to date, all died rather promptly.[328,427-431]

The only treatment available in mucormycosis is the control of the predisposing disease, such as the careful regulation of diabetics. Mucormycosis of the sinuses and orbit in two diabetic patients was successfully suppressed by careful insulin regulation,[426,432] although in one case desensitization and iodide therapy was used in addition. Another case of mucormycosis of the orbit recovered following removal of the infected eye. These three are the only cases successfully treated of several reported in the literature. Spread of the fungus from the eye or sinuses to the central nervous system

has been universally fatal.[428,433-437] Experimentally, it has been shown that the presence of uncontrolled and acidotic diabetes creates an environment where the Rhizopus fungus becomes pathogenic.[438] Cortisone and corticotropin have been shown to enhance experimental infections[430,439] and should not be employed in the treatment of mucormycosis in man.

Summary.—Available therapy to date has not given encouraging results. Desensitization of the patient with autogenous vaccine and iodide administration offer dubious help. Specific chemotherapeutic agents are not yet available. To date the sulfonamides and antibiotics have been completely ineffective in the treatment of mucormycosis. Control of the diabetic state predisposing to the infection is very important.

Summary

During the past 10 years many new and promising antibiotic and chemotherapeutic agents have become available for the treatment of the deep mycotic infections. Some appear to be specific against a single fungus, while others show broad antifungal activity. Most if not all need further clinical trial before the extent of their effectiveness can be fully ascertained. Amphotericin B appears to meet the qualifications of a broad-spectrum antibiotic against fungi.

The corticoids have no place in the treatment of chronic mycotic infections. On the other hand, patients given treatment with corticoids for some other illness not infrequently may develop an overwhelming Candida infection. Only in the acute toxic phase of certain deep mycotic infections do they possibly have a place. In such situations the corticoids should be employed in full therapeutic doses for only a short period of time and in conjunction with appropriate antifungal agents.

Conventional supportive measures are as equally important and necessary a consideration as the specific agents in the treatment of the deep mycoses. In fact, when specific therapy is lacking, supportive measures appear to have promoted spontaneous regression of the disease. Bed rest, high-caloric high-protein diets, supplemental vitamins, blood transfusions, fluids, sedatives, and oral iron should accompany any specific therapeutic program, for the optimum in treatment is obtained when nutritional deficits are corrected.

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Reviews of Internal Medicine

Syphilis

Review of the Recent Literature

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The retrospective theme of the previous syphilis review [1] has been replaced by one of evaluation of the present status of syphilis as reflected by the literature of this review period (July 1, 1956 to July 1, 1957). An editorial in the June, 1956, issue of the *British Journal of Venereal Diseases* emphasizes the need for international cooperation and interchange of knowledge in the field of venereal diseases. The *Journal*, therefore, invited leading venereologists in many countries to submit articles outlining the current venereal disease status of their countries. A valuable and interesting picture is provided by this series of articles plus others from various sources. In practically all countries the attack rate of syphilis has dropped much more rapidly than has that of gonorrhea, although public health practices vary widely in the different communities. This phenomenon remains an enigma.

In Great Britain, for the first time since 1947, the number of new syphilitic patients has risen slightly in 1955.[2] Acquired syphilis of less than one year's duration has decreased by approximately 95% since the peak year of 1946. In both male and female gonorrhea and nongonococcal urethritis continue to present major problems.

In Canada, Lossing and Allen [3] report a decline in venereal disease rates of 68% from 1946 to 1955. Syphilis has declined by 89%, gonorrhea, by only 57%. In 1944 syphilis constituted 42% of the reported total venereal disease rate, while in 1955 it comprised only 14%. In 1945, early syphilis represented 37% of all reported syphilis, but by 1955, this proportion had diminished to 7%. Syphilitic admissions, which represented 4% of the total admissions to Canadian mental hospitals in 1935, had declined tenfold, to 0.4%, by 1954. Statistical, legal, case-finding, contact-tracing, diagnostic, therapeutic, and educational activities of the Division of Venereal Disease Control of the Provincial Health Department are described. One and one-half million blood samples are serologically tested free of charge in the 10 provincial public health laboratories or in their regional branches each year in this country, with a population of 15,000,000 persons and a low syphilis rate. A high proportion of these tests is for routine preemployment, prenatal, or premarital examinations. Cardiolipin antigens are used. Since 1951, the Treponema pallidum immobilization (TPI) test has been offered without charge by the Ontario Provincial Laboratory to physicians throughout the provinces of Canada. Two additional TPI laboratories have been established recently. All in all, the Canadian program of venereal

Submitted for publication Sept. 10, 1957.

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disease control appears to be well conceived and well executed.

Booth[4] reports a similar reduction in venereal disease in Australia. He briefly and interestingly describes the "bodgies" and "widgies" who apparently contribute little to the venereal disease problem down under. The large seaports of Sydney, Melbourne, and Brisbane contribute the bulk of venereal disease on the continent. Over 90% of infections come from the amateur, while the prostitute is responsible for remarkably little infection. Centers for prophylactic treatment of male civilians have been in operation for many years in a number of cities. These centers are open continuously, are free, and are well attended. In 1955, over 17,000 males attended a single center in Sydney. It would appear that such popularity of a prophylactic station among civilians is most unusual. Booth reports that gonococcal epididymitis, arthritis, pelvic inflammatory disease, and ophthalmia are extremely rare. He states that the improvement in the venereal disease picture during the last decade has nothing to do with any improvement in human morals and that it is due almost entirely to the existence of antibiotics which are capable of speedily controlling disease and rapidly limiting spread of infection. Any interference with the use or effectiveness of these antibiotics would, therefore, cause a reversion to conditions present in the preantibiotic days.

Durel[5] presents a most interesting report on venereal disease in France. As in many other countries, early syphilis has been reduced by over 90% in the decade from 1945 to 1955, whereas blennorrhagia (urethral discharge of all types) has been reduced by only 50%. Durel believes that nongonococcal urethritis comprises 70% of cases of blennorrhagia. Treatment schedules for syphilis vary widely in France, from 1,200,000 units of PAM in a single injection to 6,000,000 to 15,000,000 units in multiple injections preceded by five injections of a mercurial preparation or followed by bismuth injections over a period of at least two years. In explanation of these long (and to Americans, sadistic) schedules, Durel states, "Patients are accustomed to a lengthy treatment and rarely default. These good habits would quickly be lost if treatment with one injection became general." He cites a handful of cases of early syphilis treated in France with apparently adequate penicillin dosage who later developed paresis, tabes, or secondary syphilis. These patients may, of course, have been reinfected subsequent to treatment, as suggested by one of the reviewers in a paper some years ago.[6] Durel then adds, "While patients are receiving bismuth, re-infection is avoided!" Durel himself favors single injection treatment with benzathine penicillin for mass treatments in countries outside France, but 12,000,000 to 20,000,000 units of penicillin for Frenchman! He feels that whenever possible, prostitutes should receive a monthly injection of 2,000,000 units of benzathine penicillin G. The continued high gonorrhea rate is explained by late diagnosis in the female and failure to treat both sexual partners simultaneously. Streptomycin is most frequently used for treatment of gonorrhea, apparently in order to avoid masking concurrently acquired syphilis. Complications have practically disappeared. Trichomonas vaginalis is considered causative in many cases of nongonococcal urethritis. Durel delineates the current laws and practices regarding prostitution.

For Sweden, where there has been excellent venereal disease reporting for many years, Tottie[7] represents an encouraging picture of syphilis and gonorrhea incidence from 1919 to 1955. Infectious syphilis has declined from about 6000 cases per year in 1919 to 150 per year in 1955, with mild upswings in the late twenties and early thirties and from 1943 to 1947. About 20,000 cases of gonorrhea were reported in 1919. From 1921 to 1942 the number per year remained below 15,000; it rose abruptly to 20,000 in 1943 and 1944 and has remained stabilized since 1951 at about 14,000 cases per year. In the absence of the development

of penicillin-resistant gonococci, Tottie suggests that long incubation periods observed in the male in recent years, mild symptoms in the male, and the use of sulfonamide drugs and antibiotics in low doses which relieve symptoms but do not cure may be responsible for the continued high level of gonococcal infection. Tottie believes that the venereal disease problem is not yet solved in Sweden.

Gjessing [8] presents a picture of the course of venereal disease in Norway that is most interesting. A graph reveals that since 1876 there have been four major peaks in the syphilis and gonorrhea rates in Oslo. It is noteworthy that he correlates the peaks with periods of economic prosperity as a result of an increase in drinking and sexual promiscuity. In the same way, he correlates the valleys with the lean years. The influence of the second world war and of the German occupation is noted. In Oslo the gonorrhea rate per 10,000 population decreased from 117 in 1946 to 16 in 1955. Since 1950 the gonorrhea rate has been only one-third of the lowest previous rate. The Oslo syphilis rate was 6.6 in 1943 and 0.6 in 1955. The author concludes that the present status of venereal diseases in Norway is satisfactory. In *Nordisk medicin* for Dec. 6, 1956, Gjessing [9] draws attention to the success with which the public health authorities have handled the administration of penicillin. "Any physician needing it for the treatment of a patient with venereal disease may secure a free supply, but he must fill in an application form for each patient. In so doing, he is encouraged to remember to report his cases to the health department. The patient receiving treatment in a public hospital does not have to pay for it, but if he fails to appear on being summoned for reexamination the police may demand an explanation of his nonappearance. The law does not, however, provide any penalty for such nonappearance."

Tucker [10] reports on the result of mass testing in Burma performed by a venereal disease control team assigned by the World Health Organization. Serologic testing of prisoners, blood donors, routine admissions to hospitals, prenatal patients, etc. suggests that well over 10% and less than 20% of the population of Burma are seroreactive. It cannot be stated how much of a contribution malaria and leprosy make to this seropositivity rate.

Rajam [11] states that there are no accurate statistical data on morbidity and mortality of venereal diseases in India, but limited information based upon numbers of patients in clinics and hospitals and from small surveys indicates that the venereal diseases, primarily syphilis, rank high as a major public health problem. Venereal syphilis, endemic syphilis (both venereal and nonvenereal), and yaws exist. Sixty to seventy per cent of syphilitics admitted to the clinics of the teaching hospitals in Madras, Calcutta, and Bombay have early infectious syphilis, and the sex ratio of these patients is three or four males to one female. It is felt, therefore, that there is a large undiscovered reservoir of infection. Twelve to fifteen per cent of cases of organic disease of the heart and blood vessels are believed to be due to syphilis, and three to five per cent of syphilis cases admitted to the hospital have meningeal or meningovascular involvement. Of over 11,000 pregnant women attending the antenatal clinics of a hospital in Madras, 6.3% were seroreactors. Of almost 6000 voluntary blood donors in Madras, 5.3% were seroreactors. In hill populations in northwestern India, the prevalence rate of syphilis varied from 5% to 50%, and over 10% of these reactors had primary or secondary syphilis. Nonvenereal syphilis acquired in childhood is apparently common in the slums of large Indian cities. Yaws, however, is not a major problem in India at this time. Facilities for diagnosis and treatment are grossly inadequate both in quantity and quality. There is almost no epidemiologic investigation, patient education, or other case-finding activity. A comprehensive plan for nationwide control of the venereal diseases is now being formulated.

But all is not rosy with respect to the incidence of syphilis. An editorial in the *New England Journal of Medicine* [12] traces the triumphant progress in the control of syphilis, which, in recent years, has led many physicians to forget how the remarkable progress was made. It was another example of "The war is over, let's go home." Maintenance-control efforts were abandoned in many states, and physicians have forgotten syphilis in the differential diagnosis. However, many thoughtful physicians cautioned against premature rejoicing that syphilis was no longer a problem. Modern control methods cannot eradicate syphilis; they can only keep it down to an irreducible minimum, since they rely solely on diagnosis and treatment. In spite of the decline in syphilis, gonorrhea has maintained a high incidence. Furthermore, here and there small epidemics of syphilis were reported, and during the fiscal year July 1, 1955, to March 31, 1956, more cases of primary and secondary syphilis were reported in the United States than in the corresponding period of the previous fiscal year. The indications are that the control effort is unable to cope with the national problem of syphilis. Since the increases in both sexes were found in 20 widely scattered states, among both Negroes and whites, and were characteristic of private as well as public treatment sources, they may well forecast large-scale increases in infectious syphilis throughout the nation. Massachusetts, an area of low syphilis prevalence, had a 20% increase in syphilis in 1951, principally in the latent and late stages. These reported rates continued without significant changes at this elevated level until the present fiscal year, when another and sharper increase was noted. There was a 59% increase in primary and secondary syphilis and 14% in early latent cases over the previous year, making an over-all increase of 30% in infectious syphilis; late latent and late syphilis increased by 17%. "The years of complacency are bearing bitter fruit." In the fourth (1957) annual statement on venereal disease control problems and programs [13] it is contended that states, territories, and cities report no subtantial improvement in program over last year, and a definite worsening of the venereal disease picture in selected areas and for the country as a whole is claimed. This report, prepared by three national organizations, is based on separate reports from all 48 states, 3 territories, and 94 of the 109 cities in the United States with populations of 100,000 or over. The survey revealed the following information about venereal disease: Rates are rising statewide in 19 states; control programs are inadequate in 35 states; teenage venereal disease is increasing in 11 states; new epidemiologic outbreaks are reported in 19 states, and armed forces personnel, transient laborers, and other mobile groups are listed by 32 states and 15 city health officers as major problems in venereal disease control. Fiumara and his associates [14] described an outbreak of syphilis and gonorrhea that occurred in a small area in Massachusetts from late 1955 to the summer of 1956. It was first uncovered by an alert general practitioner and then unfolded and controlled by organized venereal disease control efforts. Rein [15] states that syphilis is on the rise again. Twenty states and eight major cities have reported rising syphilis attack rates. The Public Health Service estimates that 1,921,000 people in the United States have syphilis requiring treatment. Many states and large cities find their venereal disease appropriations inadequate to permit an effective and progressive program. Of major concern is the fact that the high rates for primary, secondary, and early latent syphilis are in the age group of 15 to 19, reaching a peak in the 20 to 24 group. Rapidly declining rates over the past several years have prompted the optimistic demobilization of venereal disease control forces, reassignments of personnel, and reduction of case-finding and diagnostic and treatment facilities, leaving many areas without facilities to discover cases or to combat sudden outbreaks. Eighteen states have already had such outbreaks, and thirty states have poorly covered areas where such outbreaks could

and have developed. Military installations and defense plants contribute appreciably to the venereal disease problem. The transmission of syphilis through migrant laborers contributes significantly to the rise in the syphilis rate. Homosexuals appear to be an important factor in the transmission of syphilis. All patients in clinic and private practice should be subjected to an examination with the standard serologic tests for syphilis. Those seropositive reactors who present no clinical or anamnestic evidence of syphilis should then be retested with one or more of the specific serodiagnostic procedures employing T. pallidum antigens. A final diagnosis of syphilis should not be made on seropositive reactors unless confirmed by a test capable of demonstrating specific treponemal antibodies. It is emphasized that as physicians we have the diagnostic tools and the therapeutic agents to control and even eradicate syphilis, but we are failing because of our own complacency about the disease, because of neglected educational programs especially for the teen-agers, and because of lack of interest or funds to find and treat the infected person.

In the changed problem of syphilis today, Perry and his co-workers [16] of the Mayo Clinic believe that the chief concern is the absence of early syphilis, with the evaluation of positive serologic tests for syphilis. In order to appreciate the situation better, these investigators reviewed the records of all patients from whom a positive test for syphilis was obtained at the Mayo Clinic laboratories during the year 1955. The records of 1559 patients were studied. Of these, 24.2% had old syphilis seen previously at the clinic; 21.8% had previous syphilis on the first visit to the clinic; 11.3% had syphilis discovered for the first time (1955); 18.1% had nonspecific reactions; 6.0% had a situation undecided as to syphilis; no action was taken in 17.5%; in 1.0% the tests were disregarded, and in 0.1% there was a transfer of reagins. The authors, recognizing the great drop in the incidence of syphilis, feel that because of the infrequency of seeing clinical syphilis, this disease is omitted from consideration in the differential diagnosis of patients with obscure signs and symptoms. In addition, their data indicate that nonspecific reactions are important but that it is also still important to realize that in most instances a positive serologic reaction indicates syphilis. Garnier and Baillon [17] feel that serologic syphilis has increased since the use of the antibiotics. This may mean a suppression without actual control of the disease by the antibiotics used for other purposes.

The Challenge of Syphilis to Science

Thomas [18] has written a provocative and philosophical essay on the challenge of syphilis to science in the present era and has pointed out the many enigmas still facing us. He cites errors of the recent past, such as exaggeration of the number of Jarisch-Herxheimer reactions and disbelief in the phenomenon of reinfection following treatment of early syphilis. The pathogenesis of infectious relapse may be different, Thomas states, in untreated and in adequately treated patients. Immunity and the ability of the skin to react with lesions to the presence of T. pallidum are two of the factors involved. Thomas is skeptical of the practical possibilities of a vaccine but nonetheless feels that efforts to develop a vaccine should be made.

Venereology in Transition

In an address delivered in Oxford, England, Moore [19] discusses the impact of the decrease in syphilis on the venereologist (syphilologist) and on the specialty of venereology (syphilology). This specialty is a young one, hardly four decades old. Its early requirements were to gain professional respectability, to detach venereal disease from quackery, and to attract competent young doctors to the discipline. Now, in 1956, the venereologist finds himself in the position of having worked himself almost, if not quite yet, out of a job. Moore points out the lack of intellectual interest in gonor-

rhea as compared to syphilis. The American syphilologist as compared to the British venereologist devotes almost always only part time to this specialty. The remainder of his time is spent in another larger medical discipline, such as internal medicine, dermatology, or neuropsychiatry. As he sees his syphilis practice melting away, he turns more and more to his other broader specialty. The public health venereologist finds transition to other and often broader responsibilities in public health easy to accomplish. In answering his question, "What is the venereologist to do with the special talents for medical investigation which he has acquired?" Moore states that the field of chronic disease, with special emphasis on systemic lupus erythematosus, is an excellent one for the syphilologist to move into. As judged by the discussion, Moore's British audience appeared to feel that much still remains to be accomplished in the field of venereology in Great Britain.

The venereal diseases continue to receive publicity in the lay press. The Philadelphia *Sunday Bulletin* for Sept. 2, 1956, featured an editorial by Clark,[20] "V. D. Is Still a Menace." The October, 1956, *Reader's Digest*[21] presented a condensed version of a discussion published in the *New York Herald Tribune* (July 15-20, 1956), dealing with the rise in venereal diseases among teen-agers.

The physician, too, still has opportunities to study syphilis. For example, two of four cases in *Current Medical Digest*[22] for spot diagnosis involved syphilis (leukoplakia; Charcot's joint). The University of Tennessee College of Medicine and the Public Health Service sponsored the 26th Venereal Disease Postgraduate Conference for physicians, at Memphis, April 18 to 20, 1957. The course was designed to acquaint the practitioner with the latest development in diagnosis, treatment, and management of venereal disease. The Department of Obstetrics and Gynecology of Jefferson Medical College of Philadelphia held a symposium on Feb. 23, 1957, dealing with syphilis complicating pregnancy. The World Health Organization[23] has published a selection of lectures from the courses, in English and French, given at the Rotterdam Port Demonstration Center 1953-1954.

This review period saw the loss of several prominent American workers in the field of venereal disease, especially John Friend Mahoney and Charles R. Rein. Dr. Mahoney was responsible for the application of penicillin to the therapy of syphilis. Dr. Rein had contributed extensively to the field of serology and mass-treatment technique.

The Oslo study, previously reported,[24,25] has received critical analysis. Eventually the real worth of this investigation will be established. Progress in serology of syphilis still continues with observations on the "standard" tests, the Treponema pallidum immobilization test (TPI), the Treponema pallidum immune adherence test (TPIA), and the Treponema pallidum complement fixation test (TPCF) with Reiter's strain of treponemes. The changing patterns of neurosyphilis and cardiovascular syphilis are emphasized. Three reports of third-generation syphilis are reminiscent of the syphilology of the past.

According to Fiumara[26] there were 4675 armed forces personnel who contracted venereal disease and named Massachusetts as the place of encounter or exposure, or both. About 92% of the cases reported were gonorrhea. From this study it appears that the venereal control problem in Massachusetts centers about the pick-up; the prostitute was named in only 6.4% of the military cases. The results of this study emphasize the need for concentrating on better and more satisfactory contact interviewing and devising more efficient methods of venereal disease control.

Good summations and sources of information on syphilis appeared during this review period. The annual review by Wortmann[27] deals with the literature of the period of our 21st annual review. The monograph on the biology of the trepone-

matoses, by Turner and Hollander,[28] is an outstanding contribution to this problem. In 1950 the International Treponematosis Laboratory Center was established in the Department of Microbiology of The Johns Hopkins University under the joint auspices of WHO and The Johns Hopkins School of Hygiene and Public Health. As a result of this cooperative project, Turner and Hollander have produced the monograph. This work is arranged in three parts: Part I deals with the biology of treponemal infections and includes chapters on the sources of strains used during the investigations, the experimental disease in laboratory animals, factors affecting its evolution, characteristics of treponemes in vitro, immunity phenomena, and the response of treponemes to drugs. Part II, which comprises a comparative study of treponemes, discusses the characteristics of the experimental disease evoked by various strains isolated from different parts of the world, the immunological relationships between these strains, and their behavior in response to penicillin. Part III consists of a single chapter, providing a useful summary of the principal findings set forth in preceding sections. Two appendices are included: The first gives details of the isolation of strains, each strain being designated according to its geographical source, while the second supplies information on the prevention and treatment of laboratory accidents that may occur during the course of experimentation. Although much has been accomplished by these studies, several problems await elucidation. The authors of the monograph suggest a number of fields that lie open to the investigator, in the hope that the knowledge to be gained from such research will aid in the ultimate conquest of the treponematoses. These are (1) study of the adaptive and mutational patterns of the pathogenic treponemes, (2) immunochemical studies of pathogenic treponemes, (3) study of the nature of the Wassermann antibody and the mechanism of its production, (4) continued efforts to cultivate pathogenic treponemes in vitro.

History of Syphilis

Ruge[29] made an interesting discussion of 50 years of the Wassermann reaction. D'Agostino[30] prepared a short account on the great syphilographer, Ricord.

Treponema Pallidum

In view of the increasing interest in the use of spirochetal antigens for serodiagnosis, newer knowledge of the morphology and serology of T. pallidum is assuming greater importance. This is especially true of the Reiter strain.

Comparative Electron Microscope Studies of Spirochetal Morphology.—Electron-microscopical studies of T. pallidum by various workers have consistently shown the presence of a narrow band of fibrils running the length of the organism and probably responsible for its motility. Mölbert[31] asserts that in pathogenic strains of T. pallidum (Nichols and Truffi) and in T. pertenue this band, which is about 700 A. wide, constantly contains 6 fibrils, whereas in Reiter's spirochete there may be between 5 and 12, though 6 is usual. The fibrils show transverse striations similar in appearance to those of collagen fibers. He has also studied the mechanism of multiplication, which was the same in all the above strains. The point at which fission is to occur is indicated by the formation of a granule of denser material, wider than the body of the organism and traversed by the fibrillar band. This granule then becomes constricted and divides transversely, about half going to each daughter treponeme, in which it appears, after division, as a terminal granule which later disappears. Dividing forms are most numerous in 7-day-old cultures or in rabbit chancres from the 7th to 10th days, but may still be found after 21 days. Multiplication by spore production does not appear to occur. Sequeira[32] made observations by dark-field microscopy at a magnification of × 1500, which showed that living T. pallidum in early syphilis is a flat wave form and not a spiral.

Cultivation of T. Pallidum.—After a critical review of the literature and his own experience, Meinicke[33] reiterates the accepted belief that virulent T. pallidum has not yet been cultured on artificial media. Those who have reported successes in all probability had mixed cultures or have encountered saprophytic spirochetes rather than virulent T. pallidum.

Experimental Syphilis

As a reflection of the advances in clinical syphilology, experimental studies have appeared on immunity, citric acid enzymes in normal and syphilitic rabbit tissues, antibodies in syphilitic rabbit sera, resistance of T. pallidum, TPI test in experimental syphilis, effect of cortisone on syphilis, and comparative study of antibiotic compounds.

Immunity in Experimental Syphilis.—The Concept of Cellular Refusal: From previous experiments carried out at the Institut Alfred-Fournier, Paris, on immunity in rabbits infected with the Nichols strain of T. pallidum, Gastinel and his coworkers[34] concluded that resistance to reinfection is not due to any germicidal activity in the host's tissues, since the strain remained virulent for fresh rabbits for at least 8 to 10 days. In the further experiments now described, serial examinations of tissue from inoculated immune rabbits failed to show any inflammatory or phagocytic reaction around the inoculum. It is postulated that there exists a state of "cellular refusal" in which a previously infected organism refuses to accept further amounts of the infecting agent. This type of "cellular memory" is thought to be a fundamental element in immunology.

Since numerous attempts at the in vitro cultivation of pathogenic T. pallidum by various investigators have been unsuccessful, it seemed advantageous to find other approaches to the problem. T. pallidum shows an affinity for certain tissues. Tauber[35] determined the concentration, in those tissues, of enzymes of the citric acid cycle, including α-ketoglutaric oxidase, pyruvic oxidase, fumarase, aconitase, triphosphopyridine nucleotide isocitric dehydrogenase, succinic dehydrogenase, and lactic dehydrogenase. In syphilitic rabbit testes, as compared to normal rabbit testes, there was a definite decrease in amounts of pyruvic oxidase, α-ketoglutaric oxidase, aconitase, and triphosphopyridine nucleotide isocitric dehydrogenase. This is probably a general reaction to the infection. Both normal and syphilitic rabbit heart tissue showed a wide variation in aconitase activity. Syphilitic rabbit kidney tissue showed a decrease in pyruvic oxidase activity and an increase in aconitase activity as compared to that of normal tissue.

Vannier[36] fractionated a pool of 105 syphilitic rabbit serums by electrophoresis-convection, and the resultant material was tested for Wassermann reagin antibody by VDRL flocculation, tests for immobilizing antibody by the TPI test, and also for agglutinating activity. Comparison of the serologic and electrophoretic data demonstrated that the Wassermann reagin antibody is concentrated in the slow γ-globulin component and that the T. pallidum-immobilizing antibody is concentrated in the fast γ-globulin component. Therefore, the differences in antibody activity are related to differences in mobilities of γ-globulin fraction components. No sign of agglutinating activity was found in any of these fractions. This may indicate the importance of more than one antibody in the agglutination reactions.

Resistance of Specifically Sensitized T. Pallidum to Methylene Blue Stain.—Rosenau and Kent[37] have found that virulent T. pallida, which are normally stained by methylene blue, become resistant to the dye following incubation with syphilitic serum and complement. The component of syphilitic serum conferring specific resistance to methylene blue appeared to be associated if not identical with treponemal immobilizing antibody. Agreement with the TPI test is very close. The reaction provides the basis for a specific diagnostic test for syphilis (TPMB test).

The investigators believe this test has an advantage over the TPI test because it is easier to check staining than motility.

Resistance or Susceptibility of T. Pallidum to Unfavorable Factors.—Borel [38] states that any factor increasing the metabolism of T. pallidum (cocarboxylase and increased temperature) increases its susceptibility to any aggression (including specific immobilization) and any factor reducing the metabolism (chlorpromazine and decreased temperature) increases its resistance to insult. At 5 C 1.2 mg. of penicillin per milliliter gives 50% immobilization of the treponemes, whereas at 35 C only 0.06 mg. of penicillin per milliliter achieves the same result. Similar findings were seen with sulfarsphenamine and with antibody. Borel believes that many other factors may also produce the same modification of the resistance of the treponeme to immobilization.

TPI Test in Experimental Syphilis.—Gastinel and Collart [39] conclude, from the experimental syphilis standpoint, that the treponemal immobilization test seems to be essentially an antigenic reaction depending on contact, past or present, of the host with treponemes, living or dead.

Effect of Cortisone on Latent Syphilis in Rabbits and Mice.—McLeod and Magnuson [40] administered large doses of cortisone (5 or 10 mg. per kilogram of body weight) to syphilitic rabbits with infections of long duration in which antibody levels had become established and to syphilitic mice in which the infection is normally asymptomatic. They showed that large doses of cortisone depresses the immunity of syphilitic rabbits, as indicated by lowered antibody titers, increased incidence of spirochetemia, and the occurrence of infectious relapse. Similar doses of cortisone had less pronounced effects upon syphilitic mice.

Chondroitin Sulfate and Hyaluronic Acid in Syphilomas of Cortisone-Treated Rabbits.—Rice [41] reports the experimental evidence on which he based his conclusions regarding the identity and relative concentration of chondroitin sulfate and hyaluronic acid in rabbit syphilomas. He suggests that the action of cortisone on the developing syphiloma is to inhibit the incorporation of sulfate into certain hyaluronic acid or hyaluronic acid-like polysaccharides produced by the animal tissue in response to the mechanical or biochemical stimuli of the treponeme. As a consequence, the relative concentration of nonsulfated polysaccharides or hyaluronic acid is increased; this, in turn, leads to a retention of water in the syphiloma.

Comparative Study of Ten Antibiotic Compounds in the Treatment of Experimental Syphilis in Rabbits.—In a comparative study of 10 antibiotic compounds in the treatment of experimental syphilis in rabbits, Kolmer [42] found that the approximate minimal curative doses of tetracycline, chlortetracycline, bacitracin, benzathine penicillin G, chloramphenicol, erythromycin, carbomycin, polymyxin B, streptomycin, and oxytetracycline by intramuscular injection once a day for 10 days were determined in the treatment of acute experimental syphilis of rabbits. As expected, benzathine penicillin G was highest in curative activity, being 25 times more effective than oxytetracycline, which ranked second in therapeutic activity, and 50 times more effective than tetracycline, which ranked third. Chlortetracycline, bacitracin, erythromycin and carbomycin were of equal therapeutic activity and ranked fourth. Streptomycin was about 250 times less effective than benzathine penicillin G and ranked fifth, while chloramphenicol ranked sixth. The minimal curative dose of polymyxin B, if it possesses any curative activity at all in experimental syphilis, cannot be expressed, since the largest dose administered (10 mg. per kilogram, with a total dosage of 100 mg. per kilogram showed no clinical healing and persistently positive dark-field examinations. None of the compounds produced detectable swellings or necrosis at the sites of intramuscular injections, but it is both possible and probable that local reactions of varying

degree may be produced by at least some of them in the treatment of human syphilis in view of the larger doses required per body weight.

Prognosis of Syphilis

Gjestland's Oslo study[24] of the natural history of untreated syphilis detailed in the 21st annual review has been subjected to critical analysis. Colonel Harrison,[43] the grand old man of British syphilology, presented a critique of particular interest because he had criticized repeatedly in a scathing manner Bruusgaard's original study of this material in 1929. It is gratifying to see that Harrison recognizes and accepts the validity of this work of Gjestland's. He does make a number of minor criticisms. "As one who has seen the very elect mistaken when reliance has had to be placed only on clinical signs, and has seen syphilis imitated by various skin diseases, I retain some scepticism but do not think mistakes in diagnosis made any very material difference to the results recorded in the present study." About 40% of the patients under study were treated initially with potassium iodide, and Harrison refers to a study by Brown and Pearce, in 1923, which indicated that this drug caused a significant increase in resistance to syphilis in rabbits. Of the 1404 patients studied, only 216 were examined by Gjestland or under his direction. In the remainder, comprising chiefly patients dead at the time of the study, Harrison points out that reliance had to be placed on records, the accuracy of which may well have varied considerably. The disparity between the relapse rate of 84% in soldiers treated by Harrison during World War I with mercury and potassium iodide and the relapse rate of only 23% in males and 24% in females reported by Gjestland is pointed out. Harrison feels the former figure is nearer the truth. He states that there is room for scepticism as to the prognostic value of the findings in cardiovascular syphilis, inasmuch as such lesions may be missed clinically and at postmortem examination. "One cannot escape the strong suspicion that much syphilis in this Boeck material must inevitably have escaped the notice of the scrutineers. Apart from the fact that an important part of the evidence is documentary, with reliance on reports by persons who might not be very syphilis-conscious, without microscopic examination autopsy evidence may lack information." All in all, however, Harrison has a high opinion of the value of this study and states his criticisms are intended only to supplement it. Esbern Lomholt[44] has also analyzed critically Gjestland's contribution on the Oslo study of untreated syphilis. He states that although Wilhelm Boeck, in 1862; K. Grøn, in 1897, and J. Scharffenberg, in 1909, added to the understanding of the prognosis of syphilis, they were not mentioned by Gjestland. Lomholt points out that over half of the living patients were not completely examined and that in the dead patients information concerning syphilis was often lacking; since they were not known to have had the disease, they were frequently not examined for it. Gjestland is also criticized for not sticking to his basic material, the 1400 cases, but incessantly "changing the denominator." Lomholt feels that Gjestland's studies on clinical relapse confirm old well-known facts and that his controversy regarding this with certain American writers is like tilting at windmills. Lomholt criticizes Gjestland's failure to compare his findings in neurosyphilis and cardiovascular syphilis with those of Bruusgaard and expresses doubts in these stages of the disease.

Untreated Syphilis in the Male Negro.—The clinical status of 267 members of the Tuskegee study of untreated syphilis in the male Negro is summarized by Olansky and his group.[45] All of the men included were living 20 years after the study began. Particular attention is paid to the evidence of late syphilis in this group and to abnormalities of the cardiovascular system in the syphilitic and nonsyphilitic groups. Electrocardiography showed abnormalities in 33.6% of the syphilitic and in 20.4% of

the nonsyphilitic groups. Specific abnormalities found to be of significantly greater incidence in the syphilitic as compared to the nonsyphilitic group include cardiac enlargement, arteriosclerosis, abnormal blood pressure (systolic more than 150 and/or diastolic more than 90), and "cardiac chief complaint." No significant difference was found among these groups with respect to the incidence of angina, dyspnea, symptomatic arthritis, strokes, deafness, or impaired vision (nonsyphilitic). Of the 159 surviving syphilitic patients, 23 showed evidence of late syphilis. Eleven of these twenty-three had cardiovascular involvement, while the remainder were equally divided between osseous and neurosyphilis. None of these 23 had received adequate therapy at the time of this survey. Final interpretation of these findings cannot be made until the entire group has died.

Occurrence of Late Syphilis in Untreated Syphilitic Patients.—Among 4500 patients with late syphilis seen in Warsaw, Poland, from 1950 to 1955, Towpik [46] analyzed 500 who had had no previous treatment. Of these, 33% had latent syphilis; 47%, neurosyphilis; 18%, cardiovascular syphilis, and 2%, benign late syphilis. Various forms of systemic syphilis, primarily neurosyphilis and cardiovascular syphilis, coexisted in 14% of the patients. In many of those with neurosyphilis, Towpik found spontaneous lessening, or loss, of activity, as reflected by the spinal fluid findings at different levels of development of pathologic changes in the central nervous system. In eight patients with active and progressive clinical changes the spinal fluid was normal. In only 5 of 26 couples in whom it was established that infection occurred after marriage, was of the same duration, and was caused by the same strain of treponeme did the disease run a similar course. In the remainder the disease was generally milder in the female. Towpik concludes that the individual immunobiological processes of the host are the major determinants of the course of untreated syphilis.

Prognosis of Cardiovascular Syphilis.—According to an editorial in *The Lancet*,[47] it has never been conclusively proved that specific treatment prolongs life in cardiovascular syphilis. Various authors are discussed, some of whom believe it does and others who believe it does not. The difficulties in such a study lie in deciding what should be considered adequate treatment and the length of time such a study takes. In the arsenical era, when therapy involved more risk, this problem was more important than it is now. The difficulties of clinical trials in cardiovascular syphilis may mean that the ultimate answer will be provided not by the clinician but by the pathologist, and there is need for further work on the histological criteria of active syphilis in the aorta. Such studies might reveal the need to continue treatment for longer than has been customary hitherto.

Diagnosis of Syphilis

Although syphilis may have become less important as a disease problem, the information yielded by the investigations made for its diagnosis is of great importance in internal medicine. This is particularly true of biological false reactions to the test for syphilis, which continue to indicate the possibility of the existence of serious disease, e. g., systemic lupus erythematosus.

Vandow and Sobel [48] summarize the present status of the diagnosis and treatment of syphilis. They believe that diagnosis has become increasingly difficult because of the frequency of biologic false-positive serologic reactions. Considerable progress is being made toward solving this problem as a result of the recent development of a number of new laboratory tests. Four new serologic procedures and their application to the diagnosis of syphilis are discussed. These are the T. pallidum-immobilization, immune-adherence, agglutination, and complement-fixation tests. These new tests are additional diagnostic aids in special situations but have not replaced the standard serologic test for routine use. In

a study of 191 patients with positive blood tests suspected to be biologic false-positive reactions, the immobilization test was reactive in 66 (34.6%), indicating that syphilis was actually the cause of the positive serologic test in one-third of the cases. The clinical impression of a biologic false-positive reaction was confirmed in the remaining 125 patients. In patients in whom the diagnosis of latent syphilis was suggested by clinical data, this was verified in only half the patients. The schedules of treatment with penicillin and other antibiotics used by the New York City Health Department are described.

Serodiagnosis

Along with continued advances in the newer procedures for serodiagnosis of syphilis, the so-called "standard" tests are still being investigated: cardiolipin antigen,[49-52] alcoholic heart extract,[53] ox and goat antigens for Price's precipitation reaction,[54] anticomplementary reactions,[55] and cryoconcentration in serologic reactions.[56] Studies are also being pushed for quicker and cheaper tests (rapid plasma reagin [RPR]).[57]

Kahn's Universal Serologic Reaction.—According to a foreign letter in *The Journal of the American Medical Association*,[58] Gupta and Gupta studied the universal serologic reaction in 15 patients with syphilis, 106 with leprosy, 76 with eosinophilia, and 52 with visceral leishmaniasis, using as controls serum of 70 healthy persons whose Wassermann reactions and Meinicke tests were negative. The universal serologic reaction was carried out with use of Kahn's antigen diluted with varying strengths of sodium chloride, and the patterns of flocculation were noted. The reaction may show distinctive patterns of flocculation in patients with well-established visceral leishmaniasis. The reaction may also be helpful in patients with eosinophilia and leprosy, in whom serologic tests for syphilis are sometimes falsely positive. Considerable changes in Kahn's universal reaction were observed by Olitzki and Sagher[59] in 27 patients with leprosy. Three main patterns of response were described as they occurred with clinical improvement under treatment with the sulfones. The characteristic nonsymmetrical curve observed by Kahn in lepromatous leprosy appeared to occur in the earliest stages of improvement. This typical pattern was noted at least once in each of 13 patients during the course of treatment of a total of 27 patients. In an attempt to evaluate the universal serologic reaction of Kahn as an aid in the differentiation between biologic false-positivity and latent syphilis, Wilkinson[60] carried out this test on sera from 39 presumed nonsyphilitic persons, 39 patients with clinical evidence of syphilis, and 112 "problem" sera. The latter group was separated into latent syphilitics and biologic false-positive reactors by use of the TPI test. Some differences in the precipitation pattern in the universal serologic reaction were found between sera from syphilitics and sera from nonsyphilitics, but Wilkinson states that these differences were not sufficiently constant to allow undue reliance to be placed on the universal reaction as a means of distinguishing specific from nonspecific reactions. This study provides additional evidence of the lack of practical value of the universal serologic reaction.

Biologically False-Positive Serologic Reactions.—Rein and Kelcec[61] review the progress that has been made in the diagnosis of biologically false-positive serologic reactions since the introduction of specific biologic procedures. They recommend that all patients in either private or clinic practice be subjected to an examination with the standard serologic tests for syphilis. Those seropositive reactors who present no clinical or anamnestic evidence of treponemal disease should then be retested with one or more of the specific diagnostic procedures employing antigens of T. pallidum. A final diagnosis of treponemal disease, past or present, should not be made in persons with seropositive reactions unless

it is confirmed by clinical or historical evidence and/or by a test capable of demonstrating specific treponemal antibodies.

Systemic Lupus Erythematosus.—In approaching the problem of the natural history of systemic lupus erythematosus, Dubois [62] states that a study of false-positive serologic tests for syphilis gives a more reliable index of the course of the disease than just a consideration from when the final diagnosis is made. In his opinion, the majority of cases of systemic lupus erythematosus that begin merely by producing a false-positive serologic reaction follow a more benign course than the general group of patients. Only one-third of the patients with systemic lupus erythematosus have false-positive serologic reactions to the tests for syphilis. According to Moore and his group,[63] early diagnosis of systemic lupus erythematosus is difficult because of the vagueness, diffuseness, and chronicity of the disease. For this reason, those patients who chronically give a false-positive reaction to the serologic tests for syphilis aid in an understanding of the natural history, evolution, and course of at least some cases of this disease. Moore describes six patients who were treated for 23, 29, 20, 16, 18, and 14 years, respectively.

Treponemal Immobilization Test and Other New Tests

The Nelson-Mayer test (TPI) is still being given world-wide trial.[64-69] Bossak, Falcone, and Harris [70] report that modifications of the original Nelson-Mayer as to the validity of Bruusgaard's findings method for the performance of the TPI test adopted by the Venereal Disease Research Laboratory have made it possible to perform this test as a daily operating routine laboratory procedure. During a one-year period of a nationwide TPI testing service offered to state and territorial public health laboratories, more than 2800 serums from diagnostic problem cases in syphilis were submitted for testing. TPI test findings were considered in relation to the sex of patients, evidence of syphilitic infection past or present, and the clinical opinions of the physicians submitting specimens for testing.

TPI Test in Treated Syphilis.—Olansky, Harris, and Price [71] have reported the results of the TPI test five to nine years after treatment for syphilis. Of 366 patients studied, 213 were in the secondary stage at the time of original treatment. Of the patients treated only once, all treated for late latent or neurosyphilis had positive TPI tests; only 33% of those treated for secondary and 3% of those treated for seronegative primary syphilis had positive TPI tests. Relationship between current TPI and VDRL tests was studied. Sixty-six per cent of the patients with a reactive TPI test, who had originally had the diagnosis of primary or secondary syphilis, were nonreactive to the VDRL test. The percentage for late latent syphilis was 22% and for neurosyphilis, 0. The longer the duration of infection before therapy, the longer the time required for the STS to become nonreactive after treatment, and the higher the pretreatment titer, the greater the percentage of positive TPI tests. These three factors, of course, are interrelated, but Olansky and his co-workers believe that duration of infection before treatment is of greatest importance in determining whether or not immobilizing antibodies will persist in the serum. They state that a considerable number of patients will be nonreactive to the TPI test some time after adequate treatment for primary or secondary syphilis and that therefore a nonreactive result by the TPI test is less definitive in patients previously treated for syphilis than in untreated patients.

Assessment of Results of TPI Test According to Clinical Data.—Influence of Some Variables on Partial Specific Immobilization: Hardy and his associates [72] have demonstrated the influence of duration of water-bath incubation, treatment status of patient, and unequal distribution of antibody on the results of the TPI tests. They have also studied reproducibility of the test.

After 17 hours' incubation the mean per cent of immobilized treponemes in 20 tubes containing the same serum was 34%, whereas after 22 hours' incubation it was 56%. Serum from untreated patients fell to a large extent into the negative (0 to 20% of treponemes immobilized) and the strongly positive (100% immobilization) groups; serum from previously treated patients often gave 30% to 98% immobilization (doubtful and weakly positive categories). Apparently because of unequal distribution of antibody, 20 tubes containing the same serum gave a range of 42% to 88% immobilization of treponemes in the various tubes. The authors state that the different variables encountered often compensate for one another and that in actual practice the reproducibility of the qualitative test is very satisfactory.

Value of Nelson Test in Diagnosis of Congenital Syphilis in Early Infancy.—Romagny [73] throws some doubts on the absolute reliability of the treponemal immobilization (TPI) test of Nelson in the diagnosis of congenital syphilis and quotes 29 case histories, some of which seem to suggest that the TPI test may occasionally give false results. He regards the TPI test as another laboratory test, more sensitive than the STS, but with definite limitations, its greatest value being as an instrument of research into the transmission of congenital syphilis.

Detection of Syphilitic Reagin by Means of Conglutination Reaction.—In a communication from the Institut Pasteur, Paris, Faure and Daulas-Le-Bourdelles [74] describe the technique of the conglutination reaction. In a comparable study the techniques of Kline and Kolmer and the conglutination reaction were used to detect syphilitic reagin in 87 syphilitic and 274 presumably nonsyphilitic sera. Only in 3 of the 274 controls was the negative reaction in doubt. With the conglutination test the syphilitic sera gave reactions two to eight times as sensitive as those obtained with the Kolmer test; zoning, however, was frequently encountered, and for this reason the reaction should not be used for routine diagnostic purposes, though its high sensitivity may be useful in difficult cases.

T. Pallidum Immune Adherence and Hemagglutination.—Daguet [75] presents a new and reputedly simpler and easier method of reading reactions in the T. pallidum immune adherence test. In the test as originally described by Nelson, attachment of treponemes to erythrocytes in the presence of antibody and complement is measured by treponeme counts in the supernatant fluid. Daguet states that erythrocytes to which treponemes have adhered undergo agglutination, possibly because treponemes adherent to two different red cells may intertwine or because one treponeme holds two red cells together. With this modification, the sediment at the bottom of the unshaken tubes is examined. If there is a small regular disk with no agglutination, the reading is negative. A granular deposit with crenated sides is read 1+ to 4+, according to the size of the deposit.

TPI and TPIA Tests.—Carpenter, Boak, and Miller [76] carried out TPI tests on 4060 sera. Of 3934 patients with reactive STS and no history of syphilis, 2148, or 54.6%, had negative reactions to TPI tests; 1695, or 43.1%, had positive reactions, and 91, or 2.3%, had doubtful reactions. Of 400 pregnant women with reactive STS in the absence of a history of syphilis, 292, or 73.0%, showed negative results by TPI test. Of 126 patients with a history of treated syphilis, 95, or 75.4%, had positive reactions to TPI test. Some of the negative results in patients with a history of treated syphilis may be explained on the basis of adequate therapy prior to the appearance of immobilizing antibodies. TPI and TPIA tests were done on 143 sera. In the preliminary experiment on 41 of these sera, there was perfect correlation between results by both tests—agreement on positive reaction in 21 sera and on negative in 20. In the subsequent test on 102 sera, 46, or 100%, of TPI positive sera showed

positive reactions to TPIA, while 52, or 94.5%, of 55 TPI negative sera were negative to TPIA test. The remaining specimen gave doubtful reaction by TPI test, positive reaction by TPIA test. The TPIA test, on the basis of results obtained to date, offers promise as a supplement to the TPI test. Inasmuch as a killed treponemal antigen may be employed, it can be more readily adapted for use in a routine clinical laboratory. Miller and his co-workers,[77] in a later communication, report their experience with the TPIA test. They found perfect correlation with this test on 21 serum samples classed as positive and 20 classed as negative by the TPI test. The sensitivity of the TPIA test was demonstrated on 69 serum samples, 25 of which were from treated patients with a reactive STS and a positive reaction to the TPI test and 44, from patients with a reactive STS and no history of syphilis. In the former group, the TPIA test was more sensitive than the TPI test: 22 of the 25 serum samples were positive, whereas only 20 were positive in the TPI test. Perfect correlation was reported in the group of 44. The specificity of the TPIA test was observed in 79 serum samples, 26 of which were from normal patients and 53, from patients with no history of syphilis but with serum reactive to the STS. There was complete agreement between the two tests in the normal persons tested, while, of the latter group of 53 persons, 52 had negative results with both tests and 1 had serum positive in the TPIA and negative in the TPI test.

Whole T. Pallidum (Nichols Strain) in Complement-Fixation Test.—Cohen [78] described a complement-fixation reaction (WTPCF) using the whole phenolized T. pallidum (Nichols strain). The antigen was the T. pallidum immune adherence test (TPIA) antigen, standardized to contain 10 to 15 organisms per high dry field, 0.25% phenol as preservative. In syphilitic sera, the titers of the TP antibodies were higher than the titers of the reagin. Some sera from nonsyphilitic persons gave false-positive reactions with the phenolized TPIA antigen because of the presence of heterophile antibody reacting with both normal rabbit erythrocytes and treponemes. This was demonstrated by absorption with normal rabbit erythrocytes. Consequently, this WTPCF technique may be used in the diagnosis of syphilis only after preliminary absorption of the heterophile antibody. The sera Cohen examined did not include many false-positive reactors. It is possible that if such sera give a positive reaction with phenolized TPIA antigen, it may be necessary to absorb these sera with lipoid antigen before testing. Cohen concluded that the TP antibodies responsible for the WTPCF reaction were similar to, if not identical with, the TPI antibodies.

Preliminary Report on Complement-Fixation Test for Treponematosis (TWR).—Price and Whelan [79] report results of a treponemal complement-fixation test for syphilis devised by them, which they call TWR (treponemal Wassermann reaction). In addition to the usual parallel comparison with standard serologic tests, the TWR was also compared with the TPI test in 785 sera from "problem cases." Because of nonvalid tests and anticomplementary reactions, the TWR could be compared with the TPI in only 735 sera and was found to be in agreement with the TPI in 91% of these. Evaluation of new tests is best carried out in patients with clearly and definitely known diagnoses. This study, therefore, leaves much to be desired. Price and Whelan point out an advantage over the TPCF test, in which a single rabbit provides only enough antigen for 50 tests, whereas in the TWR it provides enough for about 1000 tests.

Reiter Strain T. Pallidum in Complement-Fixation Test.—The Reiter strain was used by Hamelin and Vaisman [80] in the serodiagnosis of syphilis. Ruge [81] presents a most interesting history of the Reiter treponeme, pointing out that it was first isolated by Wassermann and Ficker, in 1922, from a syphilitic chancre in a human being and remained virulent for rabbits after a series of subcultures for a limited period of time. He states that further re-

search during the past 10 years has indicated that the Reiter treponeme consists of three different antigens—a thermolabile protein antigen, a thermostable polysaccharide antigen, and a lipid antigen which is similar to that found in the usual antigens. In parallel testing of the TPI test, the Reiter antigen, and lipoidal antigens in 511 patients, with use of TPI as a baseline, Reiter antigen gave only 0.75% biologic false-positive reactions, whereas the lipoidal antigens gave 6.65%. Using the TPI test as a baseline, Wilkinson [82] has studied the RCFT (Reiter complement-fixation test) in almost 200 patients with clearly defined symptomatic syphilis, in 36 patients with conditions frequently associated with biologic false-positivity, and in over 600 patients whose syphilitic status was not known. In addition, three STS were also run in parallel. The RCFT utilizes a suspension of whole phenol-killed Reiter spirochetes. Although in almost all instances the RCFT paralleled the TPI test more closely than did the STS studied, its results were far from identical with the TPI test. The author apparently considers the RCFT a variant of standard tests for syphilis rather than a treponemal test. Preliminary studies by Cannefax and Garson [83] with the Reiter protein complement-fixation (RPCF) test showed it to be comparable in sensitivity with the T. pallidum complement-fixation (TPCF) test. It also compared favorably in specificity with the TPCF and TPI tests. The production of antigen for this procedure is relatively simple and inexpensive. An interesting feature of this study is that the RPCF test and the TPCF test detected a higher percentage of primary and secondary syphilis cases than did the TPI test. Rein, Chargin, and Kelcec [84] studied the serologic reactions of 79 patients with lupus erythematosus, of whom 46 were classified as having chronic discoid and 33, systemic lupus erythematosus (SLE). Of the 79 patients, 35 gave positive serologic reactions with one or more standard tests in their serologic battery. Of these same 79 patients, all but 3 gave negative reactions to the T. pallidum immune adherence (TPIA) test and the recently introduced T. pallidum complement-fixation (TPCF) test. A concomitant syphilitic infection was established in two of these three positive reactors. In four patients the BFP (biologic false-positive) reactions were present for one to four years before recognizable clinical manifestations of lupus erythematosus appeared.

Significance of Coombs Test in Evaluation of Serologic Reactions for Syphilis.—Lindau,[85] as a result of an investigation in which he subjected 671 blood specimens to the Coombs test and to the Wassermann test, states that syphilitic sera can give a positive Coombs test. The frequency, however, is much higher for nonspecific blood specimens. A positive Coombs test thereby argues to a certain extent for the reaction being of a false-positive nature.

Cerebrospinal Fluid

Lumbar Puncture Headache in Relation to Age of Patient and Rest After Puncture.—In an attempt to determine the effect of rest on post-lumbar-puncture headache, Rosedale [86] analyzed the incidence of headache in 345 servicemen, all of whom were under 40 years of age, and in 104 civilian patients of all ages and both sexes. The servicemen rested on the table for a few minutes, then walked a short distance to their ward and remained at rest in bed for at least 18 hours. The civilians returned to work immediately after the lumbar puncture and were not advised to rest in bed. Headache developed in 3.2% of the servicemen and in 17.3% of the civilians. Among the civilians, 28.5% of those under 40 years of age and only 7.3% of those over 40 years developed headache. We believe that comparative studies should not be done between two such dissimilar groups and that results obtained should be accepted only with great caution. Schofield [87] reports the occurrence of post-lumbar-puncture headache in 6.5% of over 2200 patients. There was no statistically significant difference between the 6.6% rate reported for males and the

6.2% rate for females. The rate was 7.2% in acquired and 0.8% in congenital syphilis. In patients with normal cerebrospinal fluids, 7.3% developed headaches, while in those with pathological fluids, only 1.8% did. In the latter group the headache rate was in inverse proportion to the severity of the cerebrospinal fluid findings, none of 88 patients with Group 3 fluids developing headache. In those with normal fluids the incidence of headaches dropped with increasing age, except for a definite rise in females at the menopause. Schofield concludes with the statement that there are probably multiple causes for post-lumbar-puncture headache.

Complement-Fixation Test Results as Affected by Contact of Spinal Fluid with Friable Cork Material.—Controlled experiments were conducted by Buchanan and his group [88] with the simplified Kolmer complement-fixation test for syphilis upon spinal fluid specimens which had previously yielded negative reactions to that test. It was found that the more intense the discoloration of the specimen from contact with the friable matter of the cork, the more likely the occurrence of a false-positive reaction. Friable material from corks was added to 172 previously nonreactive specimens of spinal fluid in amounts of 0.5 mg. per milliliter, 1.0 mg. per milliliter, and 2.0 mg. per milliliter. Of 57 specimens to which only 0.5 mg. of cork per milliliter was added, none became reactive, while the remaining 115 specimens to which larger amounts of cork were added yielded 110 false-positive reactions. The mechanism of this phenomenon is being studied. Studies are also being conducted to determine whether friable cork material has a similar effect upon the other serologic tests for syphilis. Nonfriable cork material produced no false-positive reactions. These false-positive reactions to friable cork matter may be avoided by the use of paraffin-coated or of rubber stoppers.

Clinical Manifestations

Although Duncan [89] has reported a case of vesicular syphilis occurring as a Herxheimer reaction, late syphilis has received most attention in this review period.

Late Syphilis

Syphilitic Paroxysmal Cold Hemoglobinuria.—Watson and Laurie,[90] as well as Schweitzer [91] reported cases of paroxysmal cold hemoglobinuria associated with syphilis. Schweitzer's case was one of early acute meningovascular syphilis. During the cold-induced hemolytic episodes there was a marked transient leukopenia. Intensive penicillin therapy, while improving the syphilitic manifestations, had no apparent effect on the hemolytic disorder.

Sarcoma of Skin Simulating Tertiary Syphilis.—Frank [92] reported a case of sarcoma of the skin simulating tertiary syphilis.

Gumma of Liver with Calcification.—Alergant [93] reported a case of calcification occurring in gumma of the liver. Gumma of the liver is seldom diagnosed ante mortem, although it is not so rare at autopsy. Calcification of the liver is also uncommon. This case was in a 29-year-old lorry driver who complained of swelling in the right hypochondrium. Laparotomy showed the swelling to be a hard mass in the liver. Biopsy of this mass was reported as "a benign necrotic lesion, probably a gumma." Serologic test for syphilis performed at this stage for the first time was "strongly positive." After antisyphilitic therapy, the liver became smaller, but two and one-half years later the liver edge could be readily felt a couple of fingerbreadths below the costal margin. Hippuric acid excretion remained abnormally low for several months and did not reach normal limits until some eight months after treatment was started.

Late Hepatic Syphilis.—Kellock and Laird [94] discussed the incidence, clinical features, diagnosis, treatment, and prognosis of late hepatic syphilis and presented seven cases of syphilitic disease of the liver. They advise that syphilis should be considered and serologic tests performed in all cases of hepatic enlargement. They consider a

positive sulfobromophthalein (Bromsulphalein) test the most valuable single procedure in confirming the association between syphilis and liver disease and state that because of its lack of toxicity penicillin appears to be the drug of choice.

Syphilis of Mouth and Upper Respiratory Tract.—Keogh and King[95] present a refreshing and detailed description of all syphilitic lesions of the mouth and upper respiratory tract. Both acquired and congenital syphilis are considered, as well as differential diagnosis.

Scleral Gumma.—The extremely rare occurrence of a single scleral gumma without involvement of the ciliary body was reported by Bhaduri and Basu.[96] The lesion perforated spontaneously early in its course and healed rapidly following the administration of antisyphilitic therapy. The serologic tests for syphilis were reactive.

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(To be concluded)

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Evolution of Modern Medicine

Carl Friedrich Gauss

A Genius Who Apparently Died of Arteriosclerotic Heart Disease and Congestive Heart Failure

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A complete history of medicine is more a history of errors and blunders than of success. Not long ago clinical medicine simulated, in many respects, tribal medicine of the dark jungles, which included the use of concoctions of herbs and many other substances and arbitrary medical rituals. As recently as 10 years ago, the management of subacute bacterial endocarditis was primitive and irrational, and this is still true for many diseases today. Surely, when the cure for malignant neoplasia is discovered, most of the present elaborate, expensive, yet inadequate, therapeutic procedures will seem to resemble closely the procedures of the tribal medicine man. The introduction of antibiotic drugs represented one of the greatest advancements in therapy ever achieved by man, an advancement which reduced even fairly recent therapy, control, and prevention of bacterial infections to errors, blunders, and expensive ineffective empiric procedures.

Whereas such objective reflection may be considered pessimistic, adherence to the popular point of view indicates failure to understand many of the weaknesses in man and his medicine. Surely, medical history deserves continued interest, but, remember, the writings on medical history are not necessarily objective or more reliable than some editorials encountered in the daily press, which is replete with influences of emotion, prejudice, local pride, personal friendship, and personal interest of the writer, all consciously or subconsciously introduced. Empiricism and conjecture are made to appear logical for the era, and arrogance and egoism are interpreted as personal pride and true greatness of the individual of the past. When objectively presented, however, many of their actions are expressions of ignorance and error. Nevertheless, perpetuated interest in detailed aspects of the history of medicine can serve a useful purpose: It permits more accurate evaluation of the significance of current medical activities and makes one extremely humble, reserved, cognizant of his inadequacies and inefficiencies, and aware of all that is yet to be done.

Medical history discloses a plethora of errors mingled with a paucity of cherished advancements. But this is the history of science and of man who makes it. Who would desire to return to the rather recent "great days" of medicine of less than 50 years ago and the recommendations in clinical practice of the great Sir William Osler, as recorded in Osler's first edition of medicine—the days before insulin, most vitamins and hormones, antibiotic agents, malarial control, prophylaxis of many infectious diseases, highly developed public health programs, recognition of myocardial infarction, most viral diseases and other clinical states, types of hemoglobin, and many accurate and special diagnostic and experimental proced-

Submitted for publication Sept. 30, 1957.

From the Department of Medicine, Tulane University School of Medicine.

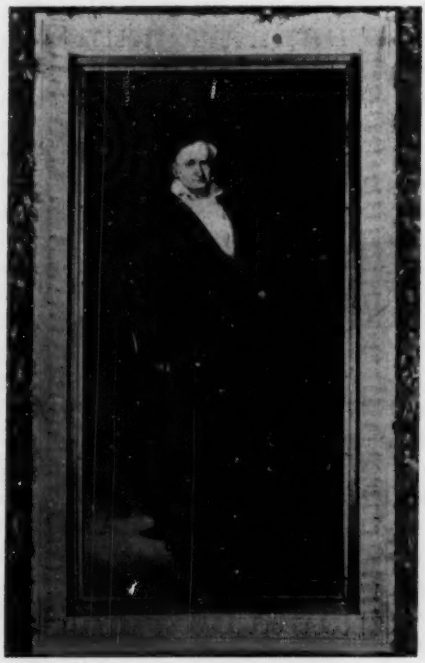
Presented before the History of Medicine Society of Tulane University School of Medicine on April 1, 1955.

ures? Although few and widely separated, the significant developments glitter in a background of failures and ignorance.

With these precautionary remarks that medical history be considered with mature reservation and reflection, I would like to tell of a *truly great man* a genius if ever there was one, an originator and creator of ideas. Not only is he of interest to those in the medical sciences because of his great mind, but also because he made important contributions that remain today of considerable value to medicine and related biologic sciences. To know people with great minds, even indirectly, is most stirring and pleasurable, an experience rarely forgotten.

Carl Friedrich Gauss (Fig. 1) was a mathematician and is, in fact, still considered the "Prince of Mathematicians," a title imprinted on the Gauss medal that his king had struck. He may have had two mental equals, Archimedes and Newton, but surely no peers. Equally capable in pure or applied science and mathematics, he applied mathematics to physics with considerable success but made his greatest accomplishments in pure mathematics. He lived at a time when several other great minds were active in Germany, namely, Goethe, Mozart, Schiller, and Beethoven, and when Voltaire and Euler were living in other nations.

Fig. 1.—Carl Friedrich Gauss, portrait by R. Wimmer in the Deutsches Museum in Munich. Reproduced with permission from Dunnington, G. W.: Carl Friedrich Gauss: Titan of Science, New York, Exposition Press, 1955.



Gauss was born of extremely poor parents in a miserable cottage in Brunswick, Germany, on April 30, 1777. His father, Gebhard Dietrick Gauss, was also the son of a poor peasant, Jurgen Goose (as the name was originally spelled), and his mother, Dorothea Benze, who was barely able to read, was the daughter of a stone cutter who died of tuberculosis at the age of 30 years. His parents were married in 1776; a year later their only child was born, Johann Friedrich Paul Gauss, who later dropped the Paul and signed his name Carl. His birthplace, 1550 Am Wendengarben, today Wilhelmstrassee 30, is a museum. At the age of 2, Gauss was recognized as a wonder child with fundamentally superior intelligence and was considered to be supernatural. His father worked as a gardener, canal tender, and bricklayer, a man without distinction, strict, harsh, and even brutal, but possessing great integrity, honesty, and perseverance. He made every effort to prevent his son from acquiring an education, and if his plans had materialized, young Gauss would have followed his father's occupation. However, through the efforts and insistence of his mother, who protected him from his father's plans and really assured the development of his mathematical genius, Carl was permitted to follow his interests, although under extremely adverse circumstances. He was forced by his father to work during the day and to sit for long hours at the spinning wheel on long winter nights. As a child, he read late at night in his attic room by the flickering lights of a wick he made with rough cotton fed with small bits of fat placed in a large hollowed turnip. His uncle, Johann Friedrich, Dorothea's brother, was an intelligent and pleas-

ant person, who recognized Gauss's great mental attributes and encouraged and assisted him in every way possible. This valuable influence, for which he was ever grateful, was recognized repeatedly by Gauss.

Unlike Archimedes and Newton, Carl exhibited his mathematical abilities in early childhood. For example, at the age of 3 years, while watching his father prepare the payroll for his laborers, he pointed out that his calculations were erroneous. Although his father was considerably irritated, his frugality forced him to check his calculations, whereupon he found them to be in error. Gauss learned arithmetic without assistance, having picked up the significance of the digits 1, 2, 3. He later indicated to his friends that he learned to calculate before he learned to talk. As a boy, he learned the pronounciation of the letters of the alphabet from his parents and then learned to read alone.

Gauss entered school after his seventh year of age. His teacher, Buttner, was a brute who used the rod freely and terrified his students. When Gauss was 10 years old, Buttner presented his class with the usual problem of long addition, 81,297, 81,495, 81,693. . . 100,899, each number increasing by 198 for a total of 100 terms, the answer to which Buttner had. It was customary for the pupil to lay his slate face down on his master's table, return to his seat, and remain quiet until all slates had been turned in. After placing the numbers for addition on the blackboard, Buttner turned, glanced at his "brats," and settled in his chair for relaxed reading. No sooner had he settled than young Gauss walked up, laid his slate down upon the table, and returned to his seat. Buttner peered scornfully over his glasses, for he knew the slate must surely contain an error, and he would be forced to thrash this newcomer, another blockhead. After all slates had been laid down, Buttner reached at the bottom for Gauss's and found it to contain only one number, the correct answer. He called Gauss before the class and asked him how he obtained that number, whereupon he displayed the concept and use of arithmetic progression, although he had never previously known that mathematical principle. Buttner soon realized Gauss was a genius and could be taught nothing in that particular class. Fortunately, Buttner had a bright young assistant, Johann Martin Christian Bartels, whose job was to assist beginners and to cut the quills. A rapid friendship developed between him and Gauss. He gave Gauss many mathematical books to read and provided him with discussions and direction.

Gauss quickly mastered the binomial theorem

$$(1+x)^n=1+\frac{n}{1}x+\frac{n(n-1)}{1\cdot 2}x^2+\frac{n(n-1)(n-2)}{1\cdot 2\cdot 3}x^3+\ldots$$

in which n is not necessarily a positive integer and may be any number. The binomial theorem had led to nonsense from noncritical use of infinite processes by many mathematicians. This caused Gauss to study numbers and to become a "rigorist," extremely critical of his own work and that of others. Because, as a student, he was dissatisfied with the proofs in his textbooks, he proceeded to improve upon them. This initiated entirely new concepts, unknown even to Newton, Leibniz, Euler, Lagrange, and Laplace, all great analysts of their times. His proof of the binomial theorem when n is not a positive integer began to change the whole aspect of mathematics and is still too advanced for textbooks of today. He was the first to point out that a proof that leads to absurdities like "minus 1 equals infinity" is no proof at all and has no place in precise mathematics.

Through the efforts of Bartels, Gauss was introduced to Carl Wilhelm Ferdinand, the Duke of Brunswick, and his court, for whom he performed his feats in mental calculations. The Duke, who recognized his rare mental qualities immediately, became his patron and provided him with opportunities for further study, including a small sum for living expenses. He studied at the Gymnasium, where his lightning mastery of the classics and languages astonished his teach-

ers and fellow students. At the age of 15, with the help of some of his older friends, he began studying the classical languages. He became proficient in several of these and even learned Russian after he reached the age of 60 years, being able to correspond in Russian with some of his mathematical friends in that country. He also tried to master Sanskrit but did not like it. He had strongly considered following a career in philology and did not definitely decide to follow mathematics until March 30, 1796, at the age of 20. The study of languages, however, remained a lifelong hobby.

Little was known of Gauss from his 14th to his 17th year. He was most probably developing his fundamental ideas. His outstanding trait for critical analysis, along with a productive and creative mind, were evident then. By the age of 18 years, Gauss had already worked out the principle of *least squares* in statistical analysis, the Gaussian curve, and other phases of probability, chance, and error in analysis of data. He studied Newton's *Principia* many times and became a great admirer of its author. While he was at college, his work with higher arithmetics made him immortal, his greatest accomplishments having been made before the age of 19. His prodigious powers for calculating were a great asset in these studies. Gauss was once interested in determining the number of digits in the period of the repeating decimal. To study this, he calculated decimal representations of all values of $\frac{1}{n}$ for $n=1$ to 1000. Although he did not find that which he sought, he discovered something infinitely greater—the law of *quadratic reciprocity*, which he was the first to prove after Legendre had failed and Euler had come upon it inductively but had not proved it. This led to improvement in mathematical nomenclature and notation and the invention of congruence. The use of equations and symbols in arithmetic, such as are used in algebra, resulted, permitting the addition of equations and easy solutions of problems.

Gauss was a shy man except when faced with mathematical and astronomical calculations. When visiting with his friends and strolling along the road or trails, he spoke little, thinking intensely all the time. He was a pleasant person, considerate of everyone, humble and modest, but powerful in mind and thought, as attested by his *Disquisitiones Arithmeticae*. He was lovable, warm, and friendly in the university life in Göttingen, and many professors of mathematics were his friends. He had no patience with people of little ability and had aversion and contempt for the pretender to knowledge who refused to admit his mistakes. His correspondence revealed his fine personal qualities. He never made a great showing; Bolyai once wrote that it was possible to be with Gauss for years without recognizing his greatness. "What a shame, that I didn't know how to open this silent 'book without a title' and read it! I didn't know how much he knew, and after he saw my temperament, he regarded me highly without knowing how insignificant I am. The passion for mathematics (not externally manifested) and our moral agreement bound us together so that while after out walking we were silent for hours at a time, each occupied by his own thoughts." (Dunnington)

Later Bolyai wrote that Gauss usually rested from his continuous quiet work in his room. He never spoke first and even remained silent on the achievement of some result. Only once did Gauss show considerable joy, and that was when he gave Bolyai the little tablet on which he calculated the septadecagon. Once, Gauss' mother asked Bolyai whether her son would amount to anything. When he replied that Gauss would be Europe's greatest mathematician, she burst into tears.

Gauss had to go to Helmstedt to use the library while working on his *Disquisitiones Arithmeticae*. He wrote eight chapters but published only seven because of the expense of publication. This great work was dedicated to the Duke of Brunswick, his patron.

A concise synthetic demonstration of mathematical treasures, this volume has been considered "the book of seven seals." It is difficult reading, even for experts, but became available to all when his friend and disciple, Peter Gustave Lejeune Dirichlet (1805-1859), first broke the seven seals. Gauss was the first to use complex and imaginary numbers well, handling them as real numbers. In a letter to him on May 31, 1804, Lagrange wrote: "Your *Disquisitiones* have raised you at once to the rank of the first mathematicians, and I regard the last section as containing the most beautiful analytical discovery that has been made for a long time. . . . Believe, sir, that no one applauds your success more sincerely than I." (Bell)

His critical, acute rigor for perfection developed even to higher levels when this masterpiece was rejected with a sneer by the French Academy of Sciences as unsatisfactory for publication. This upset him so much that he decided never to submit anything for publication until it could pass the most rigorous critical inspection. For this reason, he published little, many great ideas remaining unpublished and even not noted. In 1935, the French Academy of Science searched its records and contended that this great masterpiece had not even been submitted to them, and this, therefore, remains a controversial issue. Gauss slaved to condense his calculations to a single page to be viewed at a glance. He made most of his calculations mentally; improvements were intended for those less gifted than he. He calculated rapidly and was satisfied to make minor errors, being interested only in the over-all generalizations and objectives in the calculations. He knew what was approximately correct and noted only if a serious error was made in a detailed calculation. A painfully accurate check of his calculations would merely have wasted his valuable time and mental efforts.

When discussing the problem of publication with friends, he indicated that it was only of secondary importance to him. So many new ideas flashed through his mind that he could not control them and had time to record only a fraction of them. His discoveries, developments of proofs, and origination of mathematical concepts were really beautiful works of art. They were so perfect that nothing could be added without disfiguring the whole; such was his aim. Much of his work had to await comprehension by highly gifted mathematicians.

Gauss was a revolutionist and was responsible for mathematical inventions. His critical approach to arithmetic, his primary interest, was also focused on elementary *geometry*. At the age of 12, he looked askance at Euclidean geometry and began to study *non-Euclidean geometry*. Gauss had foreseen much of 19th-century mathematics, and if he had divulged much of what he knew, Abel and Jacob, creators of non-Euclidean geometry, could have turned their genius to other things instead of devoting much of their time to rediscoveries of things Gauss already knew before they were born. He began to fill the gaps in the *theory of numbers*, and his triumphs and masterpieces were in that field. His critical, methodical, and meticulous approach, combined with his prolific mathematic inventiveness, was a rare combination of attributes.

Gauss always had the fortunate habit, from the historical point of view, of writing along the margin and on the empty pages of his books. He even conducted abstruse research in this manner. Much was learned from him from these notes. Notes in his textbook by Remer indicated that he had to study as hard and as diligently as any less gifted student but that he went beyond his fellow students and even the author of the book. The marginalia also revealed that he used these elementary books much later in life. The fourth chapter, on primes and composite numbers, paved the way for his penetration into higher arithmetic. He was interested in the frequency of prime during the early period of his life.

He did keep a diary, which consisted of 19 small pages and 146 extremely brief

statements of discoveries and calculations, some of which were never made public. It contained more than a half dozen brief notations that would make anyone famous. Many discoveries were known to him years before others credited with them presented their ideas. All prior claims he could establish but never attempted to follow through, satisfied merely to say it was already known to him. The following entry for July 10, 1796, appeared in this diary, which was borrowed from his grandson 43 years after his death:

Eureka! num$=\Delta+\Delta+\Delta$.

This may be translated: ". . . every positive integer is the sum of three triangular numbers—such a number is one of the sequence 0, 1, 3, 6, 10, 15 . . . where each (after 0) is of the form $\frac{1}{2}\ n\ (n+1)$, n being any positive integer. Another way of saying the same thing is that every number of the form $8n+3$ is the sum of three odd squares: $3=1^2+1^2+1^2$; $11=1+1+3^2$; $19=1^2+3^2+3^2$; etc. It is not easy to prove this from scratch." (Bell) A number of such brief notations could not be solved until a decade or so later, i. e., until known mathematics had developed far enough or able mathematicians became available. Some remain unsolved to this day.

In 1801, at the age of 24, he broadened his interest to include astronomy, geodesy, and electromagnetism. Gauss became interested in the asteroid Ceres, which had caused much speculation and argument, first concerning its existence and then significance. He was asked to calculate its orbit quickly, while it still remained in the field of the telescopes of that time. This he did so precisely that the astronomers knew just when and where to locate it when it returned. His calculations have since withstood the test of time. This and other important astronomical mathematical calculations, predictions, and accomplishments were done well by him but actually represent a waste of his talents, for they could have been handled adequately by lesser men.

His achievements in applied and mathematical electromagnetism are well known even today, including the degaussian method used for protecting ships from mines during the last war, a contribution that may have saved America and the Allies and many lives. He discovered the method of sending telegraphic signals, which was responsible for the wireless, telephone, and telegraph, all revolutions in communications. Instruments in astronomy and electromagnetism were invented or improved by Gauss. A discussion of his developments and discoveries in this one field would comprise a lengthy story in itself. To Gauss, geodesy owes the heliotrope, a device for transmitting signals by reflected light. He cared little for his many inventions in electromagnetism. Although he was aware of their practical significance and worth, he was more interested in theoretic concepts, mathematics, and discoveries for their own sake and was never concerned with any remunerative aspects of these accomplishments. His collaborator in electromagnetism, Weber, recognized the importance to civilization of his funny little telegraph in Göttingen and prophesied that the world would be covered by a network of telegraph wires for transmitting messages with the speed of light.

In his ability to forget the entire world about him when in his own thoughts, he resembled both Newton and Archimedes. He could concentrate on the most intricate mathematical problem while his children were playing noisily about him and climbing over his lap. Like Newton and Archimedes, he had great capacity for precise observations and scientific inventiveness, and, in addition, he had considerable experimental ability.

The Duke increased Gauss' pension in 1805, so that he could marry Johanne Osthof of Brunswick. He expressed his feeling when he said to Wolfgang Bolyai, "Life stands before me like an eternal spring with new glittering colors." (Dunnington) Three children were born of this marriage: Joseph, who inherited his father's gift of mental calculation, Minna, and Louis. Jo-

hanne died on Oct. 11, 1809, after the birth of Louis, leaving Gauss lonely and turning his spring into winter. He married again on Aug. 4, 1810, for the sake of his children, but he never forgot his first wife. By his second wife, Minna Waldeck, he had two sons and a daughter. He did not get along well with any of his sons except Joseph. Two sons ran away from home and settled in Missouri, both starting as farmers and one becoming a prosperous merchant in St. Louis during the days of the river boats.

In 1808, his father died, and two years later his benefactor, the Duke, died tragically, while leading his troops against Napoleon. Napoleon, who was quartered at Holk, refused to honor his defeated leader but, in an immature tantrum and in vulgar language, ridiculed him as a soldier as he lay dying. The Duke was sneaked into Brunswick, and as the cart bearing him passed in front of Gauss, he saw the man who had unselfishly done so much for him and, in turn, for mankind. Were it not for the Duke, Gauss would have followed his father's trade.

With his patron dead, Gauss had to seek a means of support. He was jealously deprived of a professorship of mathematics, but this did not disappoint him, for although he enjoyed teaching the few intensely interested in mathematics as graduate students and mathematicians, he despised teaching students who were disinterested or too dull to learn. He became director of the observatory at Göttingen, a position that gave him financial support as well as opportunity for his studies. He once said: "This winter I am giving two courses of lectures to three students, of whom one is moderately prepared, the other less than moderately, and the third lacks both preparation and ability. Such are the burdens of a mathematical calling." (Bell) It was always regretted when unappreciative students took up his priceless time.

After Napoleon's victory, the French pillaged Germany and taxed all Germans for reparations. Gauss was more disturbed by the Duke's experience than by the taxation of the Germans by the French. He could not pay his tax of 2000 francs, and some of his friends suggested he appeal to Napoleon for clemency in his fine, but he would never give Napoleon this satisfaction, especially in view of the nature of Duke Ferdinand's death. All attempts at gifts to him by others were rejected. However, as a favor and privilege, Laplace, who was embarrassed that the "Prince of Mathematicians" should be so treated, paid the fine in Paris; this Gauss could not return. Nevertheless, when Napoleon fell, Gauss did not exult. He read as objectively as possible everything he could find about Napoleon's life, in an effort to understand his mind and was amused by much of his findings. With his sense of humor Gauss understood and appreciated his heroics. He was particularly interested in Napoleon's mind and philosophy, as well as some examples of his stupidity, such as his failure to employ the great minds of France and his conquered lands to assist him with his plans.

Gauss made significant advances not only in geometry, astronomy, arithmetic, and electromagnetism but also in Newton's field of attractions. When asked how he had made so many discoveries, he replied modestly, "If others would but reflect on mathematical truths as deeply and as continuously as I have, they would make my discoveries." (Bell) This is much like Newton's response to the same question of how he had made so many discoveries in astronomy: "By always thinking about them." (Bell) As Bell so aptly stated, this is not clear to the average person.

Gauss had an *involuntary* preoccupation with mathematical ideas. He would be "seized" by mathematics and suddenly go silent and, being overwhelmed by thought beyond his control, he would stand staring rigidly, oblivious to his surroundings. Later, he controlled his thoughts—or they lost control of him—and he consciously directed all his energies to the solution of a difficult

problem until he succeeded. Once he undertook a problem, he would never release it until it was solved, even though he would be solving several simultaneously. For four years he spent some time regularly trying to decide whether or not a certain sign was plus or minus. The solution finally came in a flash. Again, after spending weeks and sleepless nights with a problem, he would find, on resuming work with it at a later date, that the solution would shine clearly in his mind. The power for intense and prolonged concentration was one of his greatest abilities.

Gauss admired Newton and his work and appreciated, from his own experience, the effort that went into this work. The story of the falling apple aroused Gauss' indignation. "Silly!" he exclaimed. "Believe the story if you like, but the truth of the matter is this. A stupid, officious man asked Newton how he discovered the law of gravitation. Seeing that he had to deal with a child in intellect, and wanting to get rid of the bore, Newton answered that an apple fell and hit him on the nose. The man went away fully satisfied and completely enlightened." (Bell) This and the accomplishments of other great people emanate from hard work and not as easily as the story of the falling apple. It is only with dedicated interests in his work that anyone achieves greatness.

Gauss could not understand how Archimedes failed to discover the decimal system or an equivalent with a base similar to 10. The Greek symbolism of Archimedes would have expressed 325 as $(3\times10^2)+(2\times10)+5$. This oversight was considered by Gauss to be the greatest calamity in the history of science. To what heights would science now be raised if Archimedes had made that discovery! Imagine how his own accomplishments had been retarded without this system!

Unlike Newton, Gauss was never attracted by the rewards of public offices, although he was intensely interested in all matters of government, insurance, and finance. He visited the library and read all political news and newspapers he could find, from the *London Times* to the Göttingen local news. He was conservative, an aristocrat politically and not a reactionary. His poor family and peasant life made him appreciate the intelligence and problems of the masses. He was contemptuous of "leaders" who led people into turmoil for their own personal gains. Mob rule and political violence dismayed him. He preferred death to witnessing civil war in Germany. Foreign conquests like Napoleon's were incomprehensible madness. He believed in intelligent reforms. He could judge well, with his great brain, the ambitions of the great statesmen of Europe and their influence on men. The spectacle did not inspire his confidence.

His conservatism was ascribed to the closeness with which he stuck to his work. For the last seven years of his life, Gauss slept away from his observatory only once to attend a science meeting in Berlin, when Alexander von Humboldt wanted to show him off. He believed that a man need not travel around the world to know what was going on. Brains and ability to read newspapers (even if they lie) and government reports (especially when they lie) are sometimes better than any amount of sightseeing and hotel lobby gossip. Gauss stayed at home, read, disbelieved most of what he read, thought, and arrived at the truth. He was completely happy with his mathematics and simple recreations. He read widely of European literature and history and mastered foreign languages and new sciences as hobbies. Although English literature interested him, Shakespeare's tragedies were too much for his acute sensitiveness. He eagerly read the works of Sir Walter Scott, a contemporary, as they appeared, but the unhappy endings of *Kenilworth* made Gauss wretched for days, and he regretted ever having read the story. The astronomical slip in Sir Walter's story delighted him ("The moon rises broad in the northwest."),

and he went about for days comparing all copies he could find.

For his poetic contemporary, Lord Byron, he had an aversion. Byron's romantic good looks and affectations, which captivated the sentimental Germans and younger Englishmen but not the older men, made Gauss think him silly. Gauss was aware of Byron's histrionics and disliked him for them. "No man who guzzled good brandy and pretty women as assiduously as Byron did could be so very weary of the world as the naughty young poet with the flashing eye and the shaking hand pretended to be." Jean Paul was his favorite German poet, but Goethe and Schiller did not interest him.

Another source of Gauss' strength was his scientific serenity and his freedom from personal ambition. His only ambition was advancement of mathematics. When rivals doubted his assertions of priority—not stated boastfully, but as a fact—Gauss did not exhibit his diary but let the statement stand on its own merits. Legendre was the most outspoken of his doubters, and an experience made him Gauss' enemy for life. His publication of the method of least squares in 1806 preceded that of Gauss. In the *Theoria motus*, Gauss referred to his earlier discovery of this method. With great indignation he wrote to Gauss, accusing him of dishonesty and admonishing him that with all his great discoveries he should be decent enough not to appropriate this one. Laplace entered the quarrel, but Gauss failed to argue the point further, although he could have shown that he had sent the manuscript to Olbers in 1802 and that Legendre could verify this.

Many younger men like Cauchy published work that they considered new but that was actually old to Gauss. He read these without commenting on priority. He said no word of praise to the Frenchman, but why, if he had done this work himself years before Cauchy started? Hamilton published quaternion, work he thought new, but was well known to Gauss 30 years before. Many such things were buried in his notes, but he said nothing. Hamilton said it took him 15 years to realize that the algebraic concept $a \times b = b \times a$ was impossible in quaternion, which is concerned with rotations in space or three dimensions. Gauss did not reveal how long it took him to reach this goal; he merely recorded his success in a few pages of algebra that leave no mathematics to the imagination.

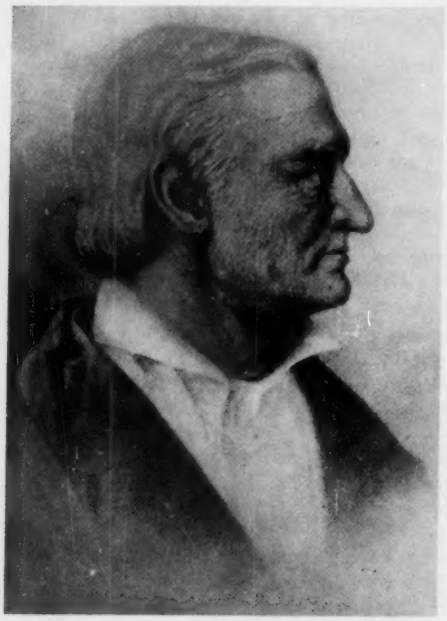
If cool in his scientific appreciation, he was cordial in his correspondence and scientific relations with those who sought him out in a spirit of disinterested inquiry. His broadmindedness toward women, for example, was remarkable for any man of his generation, especially for a German. He recommended Mlle. Sophie Germain (1776-1831), a lady mathematician, for an honorary degree, but she died before she could come to the University of Göttingen to receive it. Another Sophie, and celebrated woman mathematician, received such a degree in the liberal University of Göttingen after the University of Berlin had refused to award it to her because of her sex. This Sophie, who was enchanted by *Disquisitiones*, wrote to Gauss but, assuming he had prejudices against women, used a man's name. Gauss corresponded with her in French, addressing her as Mr. LeBlanc. Later, she dropped her guise after she did him a favor when the French invaded Hanover. This metamorphosis pleased Gauss. He was even more impressed with her intense interest in as abstract a science as mathematics.

It is not possible to relate all his accomplishments, which included mathematics, pure and applied, and the following final interests after 1800: 1800-1820, astronomy; 1820-1830, geodesy, the theory of surfaces and conformal mapping; 1830-1840, mathematical physics, especially electromagnetism, terrestrial magnetism, and theory of attraction according to Newtonian laws; 1841-1855, analysis situs and geometric functions of complex variables. His work on curved

surfaces, statistical analysis of masses of data, one of his major contributions to medicine and the biologic sciences, and investigations of the problem of generality resulted in the development of *differential geometry*. This is a study of curved surfaces in the immediate neighborhood of a point, so that the powers higher than the second can be neglected. This work enhanced geodetic research immensely.

There is much more to say of his accomplishments, but space here is limited. His last years were full of honor, but he was not as happy as he had earned the right to be (Fig. 2). His prolific, active mind was not eager for rest when illness struck him some months before his death. He had narrowly escaped death when a horse bolted on July 16, 1854, while he was watching the first railroad construction between Göttingen and Cassel. He was thrown from the carriage, unhurt but badly shocked. He recovered and had the pleasure of witnessing the opening ceremonies when the railroad reached Göttingen on July 31, 1854. This was his last day of comfort. He began to suffer with cardiac enlargement, dyspnea, and edema. Although he worked when he could, his hand became cramped, and his beautiful writing was broken at last. His last letter was to Sir David Brewster on the discovery of the electric telegraph.

Fig. 2.—Gauss in 1854. Reproduced with permission from Dunnington, G. W.: Carl Friedrich Gauss: Titan of Science, New York, Exposition Press, 1955.



Gauss was fully conscious until shortly before his peaceful death occurred, after a severe struggle to live, in the early morning of Feb. 23, 1855, in his 78th year. The year 1955 marked the 100th anniversary of Gauss' death, but he still lives everywhere. Interestingly, many other noted mathematicians have lived long lives also, i. e., Leibniz, who died at the age of 70 years; Euler, at 76; Lagrange, at 77; Laplace, at 78; Plato, at 82; Newton, at 85; Archimedes, at 75, and Pythagoras, at 99.

Thus ends the story about one of the greatest minds that ever existed on this earth. It is nice to be able to claim him for medicine, just as others claim him in other fields. It was with the process of aging and, in particular, disease of the heart that he made his fatal exit from this earth. To know of this man and to live in emulation of him can only indicate equal unselfishness and dedication to real values in medicine, to the science of medicine, and to the comfort of the sick rather than to material ends so fervently sought in a materialistic, competitive fashion. This struggle to have plenty does not recognize the fact that the greatest values in medicine come from emotional experiences with research and study, in an attempt to advance the understanding of man and, in turn, to improve his physical and mental health without consideration of anything more than happiness and opportunity of working unmolested.

Two major sources of biographic material concerning Gauss were used freely in this brief paper. From the excellent book by E. T. Bell, entitled

"Men of Mathematics," was derived a considerable amount of information, quotations, and modified comments. Another primary source of reference is C. Waldo Dunnington's "Carl Friedrich Gauss," the best single volume in English concerning this great man, about whom little has been written in the English language; it contains a thorough source of reference material on Gauss. Both books are interesting and highly recommended.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

It Pays to Be Healthy. By Robert Collier Page, M.D., F.A.C.P. Price, $4.95. Pp. 285, with 2 illustrations. Prentice-Hall, Inc., 70 Fifth Ave., New York 11, 1957.

The book is written for laymen but is applicable to all—laborer, executive, or professional folk. The theme is prevention as it relates to anything which impedes performance on and off the job. Its message does not stop there because the job is treated as a possible cause of conditions which eventually make the holding of it impossible—overextension mentally or physically. Health is definitely related to the occupational environment. In fact, the introduction printed on green paper deals with the hazards of working. Work is not deprecated, however, but practical advice is given on health for man as a worker.

The contents of the book are diverse—involving sections on normal health and the job; health problems of the business man and woman; the doctor and how he can help; health, leadership and work efficiency, and plan for retirement with health.

The author is a physician specialist in occupational medicine and a consultant to industry in man-power development. He utilizes a wealth of experience to present his philosophy on remaining healthy during gainful employment and in retirement. His style is pleasant though earthy, and his contentions are bolstered by case studies which are easily understood. This book can be read with profit by all gainfully employed persons.

FRANKLIN H. TOP.

The Surgery of Theodoric ca. A. D. 1267. Translated from the Latin by Eldridge Campbell M.D., and James Colton, M.A. Price, $5.50. Pp. 223. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York, 1955.

Many years ago I came across a choice quotation from the treatise dealing with the surgical principles and practices of Hugh or Hugo of Lucca written down by his son Theodoric toward the end of the thirteenth century. I was particularly impressed by the following words about nutrition: "Since therefore nature herself cannot bring about the manufacture of good blood without proper nutriment, nothing avails more in the healing of small as well as great wounds than the care of the nutrition of the patient. The physician must above all not be ignorant of the kind of food materials that generate good chyme and good blood. Out of such materials the wounded man must be fed in order that a suitable diet should bring about a restoration of the continuity of the wound." With considerable difficulty I was able to look up a number of points about Hugo which demonstrated the distinguished advances surgery had made in his hands under the stimulus of a vast experience in traumatic surgery of the Crusades. He opposed the notion of laudable pus. He used mild antiseptics instead of the noxious zoological concoctions rubbed into wounds by some of his contemporaries; employed a form of anesthesia and analgesia in surgical operations, and devised a contrivance similar to the Murphy button to produce intestinal anastomosis after wounds. This translation by the late Eldridge Campbell and James Colton of the first and second of four books of "The Surgery of Theodoric" will not only be welcomed by surgeons and medical historians but also should be of great interest to internists and general physicians, too many of whom believe that the great advances of medicine are coterminous with their own lives and experience. In "The Surgery of Theodoric" we find the clear light of experience perceived and wisely acted upon. For a brief period surgery rose out of the mists of the Middle Ages to a high but transitory Gothic pinnacle. Here one gets a preview of modern surgical practices, with emphasis on cleanliness, asepsis, anesthesia, nutrition, and, not least, the thoughtful care of the patient. Of course some of the prescriptions are not above reflecting the superstitions of the age, but it is well for us to remember in this time of swift medical advance that one day's accepted practice becomes the next day's disclosed heresy. A great tragedy of history, medical as well as general, is the discontinuity of learning. It requires us to go back too often and repeat all unknowingly work which had been established and put into practice many centuries ago.

It is to be hoped that this book will have a wide appeal and that James Colton will not let the lamented death of his colleague Eldridge Campbell discourage him, for he should go ahead with the translation of the remaining volumes of this fascinating work and disclose more of the remarkable wisdom of a surgeon who lived almost 700 years ahead of his time.

WILLIAM B. BEAN, M.D.

Heritable Disorders of Connective Tissue. By Victor A. McKusick, M.D. Price, $750. Pp. 224, with illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

The large majority of medical books published today are made up to a great extent of information copied from other books, monographs, and papers. Sometimes this gives us a wise distillate. Often it simply reiterates error which is long established. Many books are the musty dregs of stale data and outmoded ideas. There is a majestic inertia about communicating in medicine. Only rarely do we find a book written by someone who has made real contributions to clinical medicine through an analysis of the natural history of disease, the thoughtful study of kindreds with heritable diseases, and the evolution of a fruitful synthesis from such studies and observations. Such we have in McKusick's book entitled "Heritable Disorders of Connective Tissue." Using Sir Archibald E. Garrod, Jonathan Hutchinson, and Parkes Weber as his mentors and guides, he has explored the realms of heritable diseases of the connective tissue, inborn errors of structure which in their gross appearance were identified though not often understood long before most of what Garrod called inborn errors of metabolism were recognized. Beginning each section with a survey of the history, McKusick explores and describes his own experience with patients comprising clinical material in the Marfan's syndrome, the Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoaxanthoma elasticum, and the Hurler syndrome. He winds up with fibrodysplasia ossificans progressiva and a few very rare diseases. Many family trees are included, and there is appropriate emphasis on the genetic aspects of these syndromes. A wealth of excellent illustrations add detail and clarity which can come only from direct familiarity with the disease or careful study of photographs and reproductions of x-rays. For the connoisseur of rare diseases, this book is most interesting and valuable. It continues admirably the great tradition set by Hutchinson, Garrod, and Parkes Weber, who have emphasized the usefulness of understanding rare diseases and their natural history. It will provide valuable instruction for any physician for the reasons noted in this quotation from William Harvey, who died just over three hundred years ago. "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the unusual law of nature by careful investigation of cases of rarer form of disease."

WILLIAM B. BEAN, M.D.

Kaposi's Sarcoma. By Samuel M. Bluefarb, M.D. Edited by Arthur C. Curtis, M.D. Price, $5.50. Pp. 171, with many illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

Kaposi's sarcoma is a fascinating disease. The confusion about the nature of the disease is well illustrated in the several dozen synonyms which have been suggested since 1868, when Kaposi first described it as primary idiopathic sarcoma of the skin. Bluefarb has collected together in an elaborately illustrated book his own considerable experience, together with a multitude of reports from various parts of the world dealing with this confusing disorder. The protean manifestations, the peculiar slow progress, and the great number of remarkable complications may bring a victim of Kaposi's disease into the office of almost any specialist or general practitioner. No doubt it is not nearly as rare as reported cases would indicate. Current experiences show that it is not necessarily confined to members of the Jewish race, as was thought formerly. Whether it is primarily a bizarre variety of infectious granuloma or a neoplasm with curious granulomatous proclivities or whether it is something different is unknown. This book gives an excellent résumé and a detailed bibliography of current concepts of the disease and its natural history.

WILLIAM B. BEAN, M.D.

Nerves Explained. By Richard Asher, M.D. Price, 10s. 6d. net. Pp. 157. Faber & Faber, Ltd., 24 Russell Sq., London, W. C. 1, 1957.

Richard Asher has achieved distinction as a critic of the current medical scene, has brought many interesting insights to the average physician's view of patients, and has made many contributions to medical writings, distinguished for their thoughtful and provocative nature. In this little book, "Nerves Explained," which is addressed to laymen and physicians alike, he makes an excellent contribution to sanity and brings the warm glow of sympathy and common sense to medicine when it is beclouded by the stratospheric speculations of Freudian ideologists and fogged by the exuberant "discoveries" on the psychosomatically inclined clinical novices who too often think they are making discoveries when they are replowing already well-cultivated fields of clinical medicine. Even though fresh earth is turned up, it is the same soil in the same field. The plow now may be pulled by a tractor, but the essentials of clinical cultivation have not altered. If this wise volume could be read thoroughly and understood by many persons in our tense and distraught society some would certainly get insights to help them back on the track and others might recognize trouble quickly enough to go to a physician to obtain help. Statistics suggest that in our time a major cause of morbidity though perhaps not mortality is mental illness or nervous illness. To what extent this is inherent in our nature as it exists in and is impinged upon by our society cannot be stated. Though one cannot change the basic structure of human nature, training may lead to discipline and knowledge may lead to a sensible approach to our numerous perplexing problems. By removing his explanations from the jargons and the various clichés in psychiatry, Asher has achieved clarity while exemplifying charity. Not only will laymen profit from this book, but medical students, both undergraduate and all those who have not forgotten to be students while they are practicing medicine. It will help them to understand themselves and their patients.

WILLIAM B. BEAN, M.D.

Rypins' Medical Licensure Examinations. By Walter L. Bierring, M.D., M.A.C.P., M.R.C.P., Edin. (Hon.). Price, $10. Pp. 947. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1957.

Some years ago an inconsiderate Egyptian student shot his examiner. And why not? Examinations have been pruned in this country, and we may underestimate their influence elsewhere. In Britain, for instance, where probably a quarter of medical students come down at the intermediate or final fence, these examinations require a very considerable factual knowledge. This is commendable, but the emphasis often seems to be upon possession of the facts rather than the ability to use them, which leads to many ills. The candidate tends to study for the tests rather than for his ultimate medical knowledge, and during the last few months the forthcoming trial tends to snuff out all curiosity and originality of thought. Malleson has written that some ten per cent of students facing the major examinations develop symptoms of strain which bring them to his health center in the University of London. What is less easy to evaluate, but may be of more importance, is the long-term restriction of interest which such factual tests may induce.

Examinations, like loans and tranquilizers, may influence the donor as well as the recipient. Both the examiner's head and the curriculum may become swollen by uncritical reception of the questions, for who judges the judge? But we should remember that inquisition may do the thoughtful inquisitor a lot of good, and the future of the system may be that the academic staff will have to set examination questions which will be graded, but not answered, by their students.

The Egyptian approach is clearly not the final answer, and the student is wise to pass examinations unfailingly and in the more convertional manner. For this purpose there are many aids, which clearly and concisely cover the ground upon which questions are based. This particular volume has for years been a favorite, and this fresh edition retains it as the leader in the field. Dr. Bierring's first chapter, on medical qualifying examinations, is the penetrative analysis which we have come to expect from him, and the rest of the book maintains this high standard. The saddest comment upon examinations is that books are written specifically to help the student pass them. As the solution to this particular problem of supply and demand, this book can be unreservedly recommended to every student.

D. B. STONE, M.D.

The Clinical Aspects of Arteriosclerosis. By Seymour H. Rinzler, M.D., F.A.C.P. Price, $8.75. Pp. 339, with 57 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

The author has undertaken the task of compiling information about the clinical manifestations and treatment of atherosclerosis. Despite the use of the general term "arteriosclerosis" in the title, the author deals chiefly in this book with atherosclerosis and not generally with hyperplastic or occlusive disease of the arterioles. His approach considers atherosclerosis of the aorta and the arteries of the heart, brain, retina, limbs, and abdominal viscera as all being a part of the same disease process. Since treatment of atherosclerosis per se hinges upon a definition of causative factors, which are at present obscure, the author devotes most of the book to the management of the complications of atherosclerosis. These include angina pectoris, myocardial infarction, congestive heart failure, arrhythmias, stroke, and peripheral vascular disease. There is a complete discussion of the differential diagnosis of chest pain.

The book is described as being intended for the general practitioner. As such, it suffers from two serious drawbacks. First, the book is too largely a compilation of the literature. Over 1400 references are alluded to, some in great detail; the book itself contains only 339 pages in large type. Much of this survey will not be found helpful in the everyday management of patients. For the specialist, knowledge of this literature is better provided by other standard references in this field. A second defect is the lack of editorial guidance with reference to therapeutic measures. For example, the drug treatment of angina pectoris includes no less than eighteen agents, from cobra venom and cytochrome C to vitamin E and nitroglycerin. Similarly, sixteen drugs are discussed for the treatment of arteriosclerosis obliterans. Many of these agents, such as parenteral Dibenamine, trypsin, and tetraethylammonium chloride, are hazardous to use and are discussed with far too little editorial comment. Seldom does the author succinctly summarize either his own or the prevailing opinion regarding the best method of management of a specific clinical problem. In addition, there are occasional omissions. Despite over ten pages devoted to the treatment of arteriosclerosis obliterans of the lower extremities, the author makes no mention of the safest and probably most helpful measure, namely, progressive exercise.

If these reservations are kept in mind, the book may be of value to those physicians who do not already possess standard works in the fields of cardiology and peripheral vascular disease.

WILLIAM E. CONNOR, M.D.

Verhandlungen der deutschen Geseilschaft für Kreislaufforschung. Edited by Prof. Dr. Rudolf Thauer. Price, DM 56. Pp. 374, with 140 illustrations. Dr. Dietrich Steinkopff Verlag, Holzhof-Allee 35, (16) Darmstadt, Germany, 1956.

This is the transaction of the 1956 annual meeting of the German Society for circulation research. The topic of the meeting was functional relationship of the heart and vessel system. Lectures from the fields of physiology, pathology, and clinic gave an over-all picture of the present stand of our knowledge in this section of the circulation. How changes in peripheral dynamics affect the heart function was discussed by physiologist Reichel. Recent studies in physiology, such as Rushmer's volume elasticity determinations of the ventricles and Nylin's radioisotope examinations of the residual volume, are mentioned.

Dynamics of the vascular system were discussed by Wetterer. This investigator, known by his studies of pulse-wave transmission and by the invention of an electromagnetic flowmeter, reviewed the wave theory of the arterial ("Windkessel") system. The determination of pressure and volume curves and variations of the distensibility according to the Hamilton School, which is in some aspects contrary to the pulse-wave velocity theory of the Frank school, are thoroughly discussed.

Gauer reviewed the mechanism of the filling pressure, its relation to the stroke volume of the ventricles, and the regulation of central venous pressure. Time relations of the heart function were discussed by Blumberger. This includes the effect of different drugs on the isometric contraction and on the ejection phase, further on the filling of the ventricle. A discussion of these papers follows.

Papers of free choice include studies on the role of the tone and distention of the baroreceptors in blood pressure regulation, on oxygen uptake as a method to determine the efficiency of the heart and circulation, on the effect of distention of the abdominal aorta on the heart,

on the Bainbridge reflex, and on the role of the Bazold reflex in cardiac failure following myocardial infarction.

The second day was devoted to reviews from the field of pathologic physiology and clinic. Sjöstrand, from the Karolinska Institute in Stockholm, reported about blood-volume studies in normal persons and in persons with valvular defects and other circulatory disturbances and correlated them to other physiologic measurements and circulatory findings.

A review of secondary cardiac insufficiency due to arteriosclerosis, metabolic disorders, and infectious etiology was given by Delius. Schwiegk discussed the problem of cardiac edema and its hormonal relationship. Discussions and free choice papers from the cardiovascular field followed. The third day was devoted entirely to papers of free choice from the fields of anatomy, physiology, pharmacology, and clinic of the circulation.

One receives from the transactions a good over-all picture of the present trend of German cardiovascular research. Some of the investigations have real originality and are carried out by advanced technical instrumentarium. While there is still a remnant of the tendency of fruitless theorizing without critical investigation of the problem in some of the articles, one cannot bypass the significance of the postwar rebirth of German cardiovascular research without suffering a loss. It is recommended, therefore, that every internist interested in cardiovascular investigations and with a good command of the German language should read the transactions.

PAUL KEZDI, M.D.

Psychosomatic Medicine. Third Edition. By Edward Weiss, M.D., and O. Spurgeon English, M.D. Price, $10.50. Pp. 557, with 4 tables, 6 charts, and 11 figures. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

The first edition of "Psychosomatic Medicine," published in 1943, crystallized in simple, lucid language the basic concepts and criteria of the comprehensive approach to the ill person. Since then much has been learned, and much more written, about the influence of emotional forces on man's behavior and bodily processes. The content of this new third edition has undergone considerable change. Many sections have been rewritten, and the essence of the more recent advances has been incorporated to bring the material up to date. Fortunately the original clarity and simplicity of presentation have been well preserved and still provide the general physician with a ready reference to this changing and confusing field that he can readily understand. The format has been rearranged as well with the material of a general nature, five chapters in all, making up Part I, whereas those problems relating to the various body systems and specialties are grouped in the fifteen chapters that comprise Part II. The text is liberally sprinkled with case reports that illustrate the common problems of daily practice and explain the various diagnostic and therapeutic maneuvers that have proved most effective.

The authors attempt to maintain an eclectic approach and discuss in some detail the pros and cons of the various schools of thought. There is perhaps a little too much emphasis on the tenets and techniques of psychoanalysis, which may leave some readers with the notion that their therapeutic scope encompasses little more than superficial reassurance and similar inadequate measures. Such is certainly not the case, and I am sure the authors did not intend to convey this impression.

It is stated, on page 58, that "disturbed emotions may disturb bodily functions, not only temporarily but permanently, so that finally even structural changes may occur." This may well be true but has yet to be validated. To my knowledge it has not been clearly demonstrated that psychic factors per se can cause permanent structural lesions. Moreover, many would take issue with the thesis that emotions cause bodily changes. On the contrary, there is considerable evidence that these alterations in feelings and bodily functions occur at the same time as related aspects of a total reaction pattern, rather than in sequence with the somatic phenomena secondary to the psychic changes. There is a too common tendency to confuse the terms "psychosomatic" and "psychogenic," when, in actual fact, the former does not carry with it any causal connotation. The pathological consequences of emotional forces have gained considerable recognition, but their full potential has still to be clarified. For the present it must be clearly kept in mind that it is one matter for such factors to influence the course of an "organic" illness but quite another for them to serve as its initial cause.

These few points in no way detract from the true worth of this text. It is outstanding in its field and will provide informative and stimulating reading for both generalists and special-

ists. It should be a "must" in every undergraduate curriculum to balance the mechanistic and overspecialistic trends in modern teaching and to provoke each student to ponder the full significance of "the person in the patient."

BERNARD I. LEWIS, M.D.

Psychopathic Personalities. By Harold Palmer, M.D. Price, $4.75. Pp. 179. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1957.

Understanding Human Behavior. By James L. McCartney, M.D. Price, $3.50. Pp. 258, with illustrations. Vantage Press, 120 W. 31st St., New York 1, 1956.

Inflexible opponents of psychiatry, before passing to the next book review, might consider the words of Oliver Cromwell in a letter to the General Assembly of the Church of Scotland in 1650: "Gentlemen, I beseech you, in the bowels of Christ, think it possible that you may be mistaken."

The title "Psychopathic Personalities" misleads, for these nine delightful essays discuss the nature and character of the major neurotic and psychotic syndromes as well as psychopathy. The author is clearly inspired by William James and influenced but not bludgeoned by Freud; he writes with a clarity and conciseness that would be startling in any physician and is glittering in a psychiatrist. This is neither a textbook of diagnosis or treatment nor a tract from any one school; it is a reflective discourse from a wise thinker. I warmly recommend it.

Quotations from "Understanding Human Behavior" are "The process of birth . . . does something to the personality. It may cause very serious emotional injury to the child. . . . At the time of menstruation, the (posterior pituitary) gland may swell and so fill the bony well in which it rests that it causes an intense headache. After menstruation has started, the secretion is used up, and the headache relaxes." On page 228 the author writes, "Psychiatry has no battle with straight thinking and scientific reasoning." One would hope not, for this book represents neither.

DAVID STONE, M.D.

Alcoholism: A Treatment Guide for General Practitioners. By Donald W. Hewitt, M.D. Price, $3. Pp. 112, with 2 charts. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1957.

The Hangover. By Benjamin Karpman, M.D. Price, not given. Pp. 531, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

"I feel no pain now mother dear
But oh, I am so dry!
Please take me to a brewery
And leave me there to die"
Old Sea Shanty

"Alcoholism" gives the practicing physician a clear and usable text on the treatment of this disease. The author describes the general understanding of the problem, the management of the acute illness, follow-up, aversion and Antabuse therapy, the pitfalls of drugs, and advice to the family. It presents neither new concepts nor original work, but it is a modern and explicit treatment guide, written by a practical physician who has tried the old and the new and who avoids controversy and speculation. It tells us what to do and when and how to do it.

"The Hangover," by the chief psychotherapist at St. Elizabeth's Hospital, Washington, D. C., is a study of the psychodynamics of this illness. Nearly all chronic alcoholics agree that, as their path descends, so the physical complaints of the hangover are overshadowed by increasingly complicated emotional symptoms. The author believes that analysis of the morning after may reveal much of interest to the psychodynamically oriented psychiatrist. He records fully, and interprets briefly, the intimate account of fourteen patient's hangovers. In the last chapters he blends and contrasts the stories and ends with a synopsis. This book, which is not for those with rigid minds, adds to the accumulated knowledge of this condition and will interest students of personality and behavior disorders.

Ninety per cent of those who drink do not become pathologically addicted, but in this country, alcoholics number 4,500,000 and increase by 200,000 annually; comparable figures for diabetes meliitus are 1,500,000 and 55,000. Jellinek, at the Yale School for Alcoholic

Studies, has said that sixty per cent of drinkers are originally "normal" personalities and that any normal person may become an alcoholic. These patients are sick, and they respond to treatment; but the therapy of alcoholism, like that of peptic ulcer, requires time and patience, for there is no "miracle cure". General practitioners or internists who wish to deal with these patients should read the first of these books.

D. B. STONE, M.D.

The Physician as Man of Letters, Science and Action. Second edition. By Thomas Kirkpatrick Monro, M.D. Price, 21 s. net. Pp. 259. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh 1, 1951.

Monro's compilation of brief biographical sketches of physicians who established themselves as highly talented men or as geniuses in nonmedical lines is a rich repository of miscellaneous information. This is a book for those who go into an old bookshop and forget what they were aiming for or escaping from. It probably should have been entitled "The British Physician as a Man of Letters, Action and Science," since reference to doctors of other lands is fragmentary, perfunctory, and illiterate. In the pages of this little book I discovered diseases bearing the names of saints, a Dr. Morrison who invented a telegraph in 1753, M.D.'s who achieved their most conspicuous fame as pirates or murderers, others who forsook medicine for the church or who went in the opposite direction, and a doctor who constructed (1) a wooden bull that bellowed, (2) an automatic dragon, and (3) a self-performing lyre! Perhaps this is what we need today. We learn of Dr. Cheyne, a physician of incorrigible obesity, who wrote a well-known book on regimen and advised people about dieting, of John Radcliffe, of whom it was said that many people pretended to be ill that they might consult him and enjoy his witty conversation. The book is full of such interesting nuggets as the fact that Goldsmith introduced Auenbrugger's "Treatise on Percussion of the Chest" to physicians in England by a review of that work he wrote in 1762, the year after its publication, though this was long forgotten before Corvisart translated it into French without claiming that he wrote it or invented it. Despite its relatively limited scope, this book is an excellent introduction to the problem of physicians whose greatness was not just in the field of medicine or not in that field at all.

WILLIAM B. BEAN, M.D.

How to Keep Fit and Like It. By Arthur H. Steinhaus, Ph.D. Price, $0.50. Pp. 71, with many illustrations. Dartnell Corporation, 4660 Ravenswood Ave., Chicago 40, 1957.

Anyone who has made even casual observations about physical activity, endurance, and general work capacity in various parts of the world realizes that modern Americans from youth to old age are often in a nice jelly-like state of physical fitness compared to those in other parts of the world. Work is not pleasant for those whose forebears depended on work. Physical activity of any kind has become repugnant to so many young people that they are unable to walk a few blocks to sit at work. Their indulgence in sports with a few anthropoid exceptions is that of the spectator at gladiatorial contests. When they become obese and flatulent their tendency to react poorly when disease hits is well recognized. I doubt very much if this book on how to keep fit will have any effect at all on our culture where it is needed most, but if anyone is inclined to exercise himself back to a state of more abundant health, this book gives ample instructions which are very specific and straightforward. They are detailed enough in several categories that almost everyone so beset could benefit from following the instructions.

The concept of fitness and physical fitness has always posed a problem in semantics, in definition, and in general comprehension. Fitness depends upon a number of factors. There must be the bodily structure of physique; the physiochemical organization at the correct pitch for proper function; training, and skill. In any measure of a particular performance these must be distinguished. Finally, and the most difficult to measure or estimate, is morale, the will to work, the wish to accomplish a particular form of activity. Still and all, it must not be assumed that fitness is some amorphous state, intangible and ineluctable, which can be applied to one thing or the other. Someone well trained in running is able to swim more effectively than if he has not been so trained in running, the ability to swim being the same in both cases. Nonetheless, the crux of fitness is to define it precisely and explicitly in terms of the act to be done. Without going into a long discussion of the problem this book gives clear ideas about how fitness in general might be improved and how the race and the nation

be improved. If a thousand persons read the book, one might actually improve his fitness and become a square in the round holes of ennui bred of the material largess of the television age, where the supreme effort is to get up and turn off the machine.

WILLIAM B. BEAN, M.D.

Parkinson's Law, and Other Studies in Administration. By Prof. C. Northcote Parkinson. Price, $3. Pp. 113, with illustrations by Robert C. Osborn. Houghton Mifflin Company, 2 Park St., Boston 7, 1957.

We have seen a spate of books dealing with the inevitable confusions and frustrations of a society in which institutions proliferate at a rate far faster than any faint improvement in the moral or intellectual capacities of man. We have been told about these in "The Managerial Revolution" and "The Organization Man." Medical people long familiar with Parkinsonism, Parkinson's disease, or Parkinson's syndrome will be pleased to learn of the recent discovery and mathematical demonstration of Parkinson's law. In any event, a citizen purporting to be one C. Northcote Parkinson, "Raffles Professor of History at the University of Malaya," defines briefly and in Parkinson's own and splendid style, Parkinson's law. It holds that in any administrative organization, administrators multiply at a rate of increase of approximately six per cent per annum no matter what. His derivation of the formula shows mathematical genius of a kind never quite achieved by Einstein. Basing his original observations on the contemporary discovery that in all recent warfare the number of the enemy killed varies inversely with the number of generals on one's own side, he takes off from there. He elaborates upon this theme, using the illegibility of signatures as an example, though he has not yet brought his mathematical genius to bear on the exact point in a successful executive career at which handwriting becomes meaningless even to the executive himself. The meeting of committees and their role is stressed by demonstrating that the time spent on any item of high finance will be in inverse proportion to the sum involved. The size of governing cabinets has led him close to final solution and disposal of the coefficient of inefficiency. He deals some lethal blows at the ordeal by houseparty as method of selecting people for anything, pointing out that "the persons who satisfy this type of examiner are usually of a cautious and suspicious temperament, pedantic and smug, saying little and doing nothing."

One of the most important discoveries in Parkinson's classic little volume is the demonstration that a magnificent building, all marble, chrome, and glitter, is an infallible diagnostic sign that the institution has not only lost its major function but is fast losing contact with reality. This is the reciprocal of a law which determines the importance of the individual person in an heirarchy where the number of doors to be passed, the number of personal assistants, and the number of telephone receivers, added to the depth of the carpet in centimeters, is a good algebraic function of the illusion of importance. This enables one to derive a person's self-importance with stunning accuracy. How to orient yourself in the clockwise centrifugal flow at a cocktail party is well worked out. The dry rot in administrative life characterized by that numerous tribe with a high concentration of incompetence and jealousy and the unhappy eventuation in clinical injelititis or palsy paralysis is another elegantly described and clearly delineated syndrome which seems to have escaped the attention of administrative experts and inefficiency experts these many years. Whether one is on the inside of an institution or peers through the bars from the outside, an understanding of Parkinson's Law will help him comprehend how the little wheels which turn the big wheels always move in the opposite direction.

WILLIAM B. BEAN, M.D.

Der Rheumatismus: Vol. III. Spondylitis ankylopoetica (Morbus Strümpell-Marie-Bechterew). By Viktor R. Ott and Hans Wurm. Edited by Rudolf Schoen. Price, DM 38. Pp. 258, with 137 illustrations. Dr. Dietrich Stienkopff Verlag, Holzhof-Allee 35, (16) Darmstadt, Germany, 1957.

The combined efforts of a clinician and a pathologist produced as exhaustive treatise packed with concentrated information on spondylitis ankylopoietica, also known as morbus Strümpell-Marie-Bechterew. Ott introduces the first part of the volume with the historical development of the clinical concept of this disease, its terminology, and the description of its classical appearance, whereby he equips the reader with the necessary knowledge and curiosity to absorb the contents of the volume with great interest. The examination of the patient, the characteristics of the onset and progress of the disease, the radiological findings—

especially the changes on the sacroiliac joint—and the statistical data are worked out in the minutest details. With the exception of the increased sedimentation rate, the laboratory methods are considered insignificant in their diagnostic value. The disease is clearly differentiated from other degenerative, inflammatory, and metabolic diseases of the spine. Inheritance and infections as etiological factors are subjected to a critical discussion. Butazolidin, salicylates, corticotropin (ACTH), and steroids, roentgen and physical therapy are thoroughly evaluated as therapeutic measures, with explanatory warnings against the undesirable side-effects of these media. The treatment is effective in the initial stages of the disease but ineffective in the fully developed disease. Therefore, an early diagnosis is mandatory for a successful therapy.

Wurm introduces the second part of the volumes with an interestingly detailed normal anatomy of the vertebrae, the intervertebral disk, and the intervertebral, costovertebral, and sacroiliac joints, followed by a scholarly exact description of the various details of the pathology and pathogenesis of spondylitis ankylopoietica as it affects each individual component of the spine and progresses in a caudocranial direction. The process begins with changes in the sacroiliac points, followed by extra-articular ossifications of the joint capsules and ligaments, whereby the annulus fibrosus is considered as a joint capsule and is concluded by the intra-articular bony fusion of the articulating surfaces. Several new concepts of the pathogenesis of the fusion of the vertebrae and the ossification of the longitudinal ligaments are introduced by the author with documentation by excellent photographs of macerated spines and histological sections of the described changes. The appropriate selection of the illustrations, abundant in quality and quantity, deserves special mention.

Both authors succeed in offering to the beginner the fundamentals of spondylitis ankylopietica as well as in offering specialized details to the experienced expert. Both the general practitioner and the specialist will not only read but also study this volume with great profit.

GUSTAV ZECHEL, M.D.

Prevention of Chronic Illness: Chronic Illness in the United States. Volume I. Commission of Chronic Illness. Price, $6. Pp. 323. Published for the Commonwealth Fund by Harvard University Press, Cambridge 38, Mass., 1955.

In 1946, four national professional organizations—the American Medical Association, American Hospital Association, American Public Health Association, and American Public Welfare Association—formed a Joint Commission on Chronic Disease. When the National Health Assembly in 1948 brought out the fact that chronic disease is the nation's number one medical problem, this joint commission in 1949 was formed into a new voluntary organization, the Commission on Chronic Illness, to study the problems of chronic disease, illness, and disability.

It is understandable that one of the first projects of the Commission on Chronic Illness was to hold a National Conference on the Preventive Aspects of Chronic Disease. As early as 1947 the four national sponsoring organizations for the Commission on Chronic Illness had said, "The basic approach to chronic disease must be preventive. Otherwise the problems created by chronic diseases will grow larger with time, and the hope of any substantial decline in their incidence and severity will be postponed for many years."

The sentence above is the opening sentence of this book, "Prevention of Chronic Illness," and is the thesis which is constantly expounded throughout its 323 pages.

The National Conference on Preventive Aspects of Chronic Disease held in 1951 developed a list of long-term diseases and conditions which could be largely controlled if full utilization was made nationally of the knowledge which existed about these diseases and conditions in 1951. This list included diabetes mellitus, pernicious anemia, syphilis, hyperthyroidism, myxedema, hyperparathyroidism, sprue, "alcoholic" neuritis, pellagra, beri-beri, scurvy, rickets, hookworm infestation, malaria, amebiasis, thrombocytopenic purpura, and familial hemolytic jaundice.

Another twenty-seven diseases and conditions, with long-term manifestations, were considered as being "only partially controllable."

A third group, of seven illnesses, with a tremendous potential for causing premature mortality and long-term illness—certain congenital defects, certain neurological diseases, certain psychoses, certain neoplasms, chronic glomerular nephritis, hypertension, and arteriosclerosis—was described as still "largely uncontrollable."

Part I of this book presents twenty-one conclusions and recommendations concerning prevention of chronic illness adopted by the Commission in 1956, the year the Commission ended its work. Grouped around such headings as promotion of health, primary prevention, secondary prevention through periodic health examinations, secondary prevention through screening examinations, personnel and education and community planning, these problems are or should be of concern to all internists. They are problems which directly affect the abilities of internists in meeting the problems of their patients daily. Unfortunately, far too many internists consider themselves far too busy to give real thought to their own personal contributions to these problems. This section of "Prevention of Chronic Illness" is most useful in that it gives the busy internist an opportunity to gain a perspective on these problems which he cannot gain through his own personal practice.

Part II of this book holds less significance for the internist than Part I, for it consists of summaries of information on prevention of selected chronic diseases and contributory factors. Most internists are familiar with the material covered in Part II. Again, however, these summaries give a perspective with emphasis on prevention which some physicians are inclined to overlook.

As with all of the volumes published for the Commonwealth Fund by the Harvard University Press, this book has been carefully edited.

HOWARD A. RUSK, M.D.

Obesity: Its Cause, Classification, and Care. By E. Philip Gelvin, M.D., F.A.C.P., and Thomas H. McGavack, M.D., F.A.C.P. Price, $3.50. Pp. 146, with 6 figures and 14 tables. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers) 49 E. 33d St. New York 16, 1957.

At first glance one is tempted to ridicule the subtitle of this book, since the cause and treatment of obesity seem obvious. On closer examination, however, it becomes apparent that the authors have carefully classified obesity in all of its manifestations. They discuss several methods for estimating the degree of fatness of a patient and the metabolic processes that result in deposition of adipose tissue.

In the chapter on the classification of obesity they discuss such terms as "nervous obesity, endocrine obesity, hereditary obesity, and habit obesity." They rightly surmised that no classification is wholly satisfactory.

In discussing the factors which regulate the appetite and secondarily the amount of food ingested, they conclude that this regulation is "exceedingly complicated." Etiologic factors are discussed in somewhat greater detail. With the exception of the rare patient who truly has an endocrine problem, these can be summed up by describing the various classifications as each being due to a disproportion between the amount of food eaten and the amount of energy expended.

The management of obesity is yet another matter. Here the authors do an admirable job of describing the role of the physician in preparing the patient psychologically in advising him on such matters as exercise, the use of adjuvant drugs, and the management of his everyday eating habits. Perhaps the most important phase of this management is the follow-up care of the patient who has been given a diet, for the true success or failure must be determined not by the number of pounds lost but by the weight and condition of the patient a year or more after the institution of therapy.

This book does not present any striking or novel solutions to the problem of obesity, but it does provide a good point of reference for the practicing physician and the advice contained within it is sound.

ROBERT E. HODGES, M.D.

Symposium on Endocrines and Nutrition. No. 15. Proceedings of the Nutrition Symposium held at the University of Michigan Medical School Oct. 11-12, 1956. Edited by Frank H. Bethell. Price, $2.50. Pp. 104, with illustrations. National Vitamin Foundation, Inc., 149 E. 78th St., New York 21, 1957.

This volume described a meeting held at Ann Arbor, Mich., in October, 1956, which in turn describes work which was done in 1955 and 1956 and in previous years. I read the report of the symposium in October and am writing this review in November, 1957, and it will appear in print sometime in the late winter or spring of 1958. In this day of instantaneous dissemination of "news?" by mass media, I am far from decrying the slow turning of the wheels.

I am not sure, however, that some of the preliminary announcements of work and discovery urged on by firms which wish to develop and exploit new products might not be reduced if medicine's communications were improved and the inertia could be diminished somewhat.

In this symposium there are excellent discussions of the role of nutrition and liver disease, on endocrine imbalances, steroids, adrenal steroids, effect of humeral factors on hematopoiesis and digestion, and reports of progress in field of insulin fatty acids and many other topics. Much emphasis is placed on the intimate detailed and very important relationships between vitamins and hormones, between various essential nutrients and those humeral factors which determine the background metabolic situation which permits the energy transfers and fabrication of new tissue concerned in the processes of life itself. In an increasingly complex field, symposia such as this enable physicians and investigators to get a good running view of fields of activity separate from their own and thus avoid at least some bewilderment inevitable in a time of increasingly complexity.

WILLIAM B. BEAN, M.D.

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News and Comment

ANNOUNCEMENTS

Survey of Compounds Which Have Been Tested for Carcinogenic Activity.—Supplement I to "Survey of Compounds Which Have Been Tested for Carcinogenic Activity" is now available. The publication lists 981 compounds which were tested during the period 1948 through 1953. Data were collected and classified by Prof. Philippe Shubik, of the Chicago Medical School, and Dr. Jonathan Hartwell of the National Cancer Institute. Of the total number tested, 779 are reported for the first time in these tests. Copies of the new publication are available from the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. at $3.50 each.

World Congress of Gastroenterology.—The program for the scientific session of the World Congress of Gastroenterology is now being fully developed, and the following are the participants in the five main symposia:

Peptic Ulcer: R. Boller (Austria), J. De La Vega (Mexico), F. Avery Jones (Great Britain), S. M. Jordan (U. S. A.), G. Katsch (Germany), A. Lambling (France), J. Parparcen (Venezuela), T. Raghaven (India), G. Siffert (Brazil), B. Wissmer (Switzerland).

Intestinal Infections and Infestations: E. Neter (U. S. A.), N. Svartz (Sweden), J. Taylor (Great Britain), J. Basneuvo (Cuba), M. Brooke (U. S. A.), A. Cruz and O. Peralta (Chile), R. Elsdon-Dew (South Africa), E. C. Faust (Colombia), L. Leon (Ecuador), P. Yekutiel (Israel), R. Fournier (Mexico).

Malabsorption: E. Wollaeger (U. S. A.), H. Weijers and J. Van de Kamer (Netherlands), F. Hernandez-Morales (Puerto Rico), M. Shiner (Great Britain), F. Milanes (Cuba), J. French (Great Britain), A. Frazer (Great Britain), C. Butterworth (U. S. A.), D. Adlersberg (U. S. A.), R. Blomstrand (Sweden), S. J. Baker (India).

Nutrition and Its Effect on the Liver and Pancreas: C. H. Best (Canada), J. Caroli (France), C. Davidson (U. S. A.), J. Davies (East Africa), H. Ducci (Chile), N. Scrimshaw (Guatemala), B. Sepulveda and S. Zubiran (Mexico), S. Sherlock (Great Britain), J. Waterlow (British West Indies), I. Wood (Australia).

Gastric Carcinoma: H. Berg (Germany), J. Maisin (Belgium), H. Mogena (Spain), I. Ravdin (U. S. A.), L. Rigler (U. S. A.), H. Stewart (U. S. A.), I. Velez-Escobar (Colombia), J. Clemmesen (Denmark), R. A. Gutmann (France), Y. Tazaki (Japan).

In addition, over 150 papers have been accepted by the program committee for free presentation. Representation, on important scientific topics, will be made from Argentina, Australia, Belgium, Brazil, British West Indies, Canada, Chile, Colombia, Cuba, Denmark, El Salvador, Dominican Republic, Egypt, France, Germany, Great Britain, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Morocco, Netherlands, Norway, Paraguay, Peru, Poland, Portugal, Puerto Rico, Rumania, South Africa, Spain, Sweden, Switzerland, Syria and the United States of America.

As of this date, over 200 persons are scheduled to appear on the program. This includes 36 from the United States and the remainder from 43 other countries.

For hotel reservations, contact the World Congress of Gastroenterology Housing Bureau, 1616 K St., N. W., Washington 6, D. C. Reservations will be available at the Sheraton Park and Shoreham Hotels.

For information relative to the World Congress of Gastroenterology, attendance, accommodations, registration, program, activities, etc., contact Dr. H. Marvin Pollard, Secretary General, World Congress of Gastroenterology, University Hospital, Ann Arbor, Mich.

The annual scientific meeting of the host organization, the American Gastroenterological Association, will immediately follow the meeting of the World Congress in the same hotels and utilize the simultaneous interpretation facilities. The meeting will be held on Friday, May 30 and Saturday, May 31, 1958.

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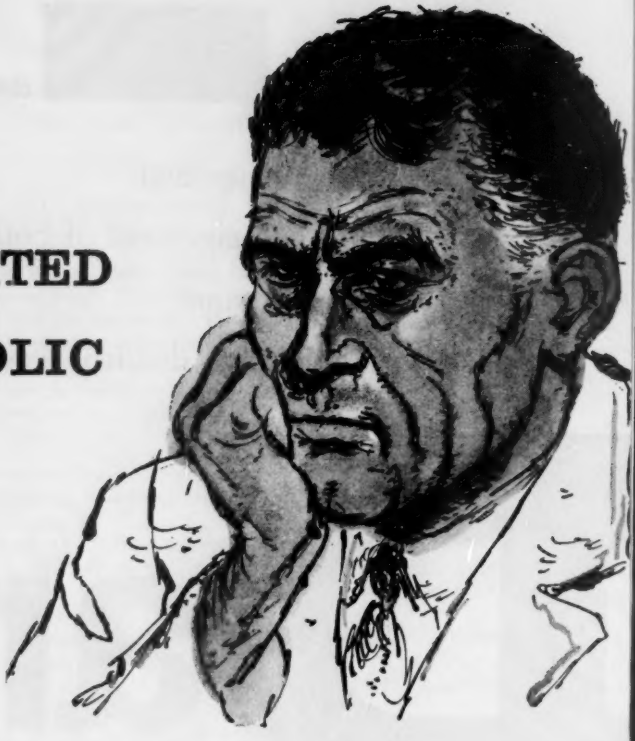

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*Smith, J.A.: *J.A.M.A.* 152:384, May 30, 1953. Brown, W.T., and Smith, J.A.: *South. M. J.* 46:582, June, 1953. Smith, J.A.: *Postgrad. Med.* 16:316, Oct., 1954. McCullagh, W.H.: *J. Florida M.A.* 41:718, Mar., 1955.

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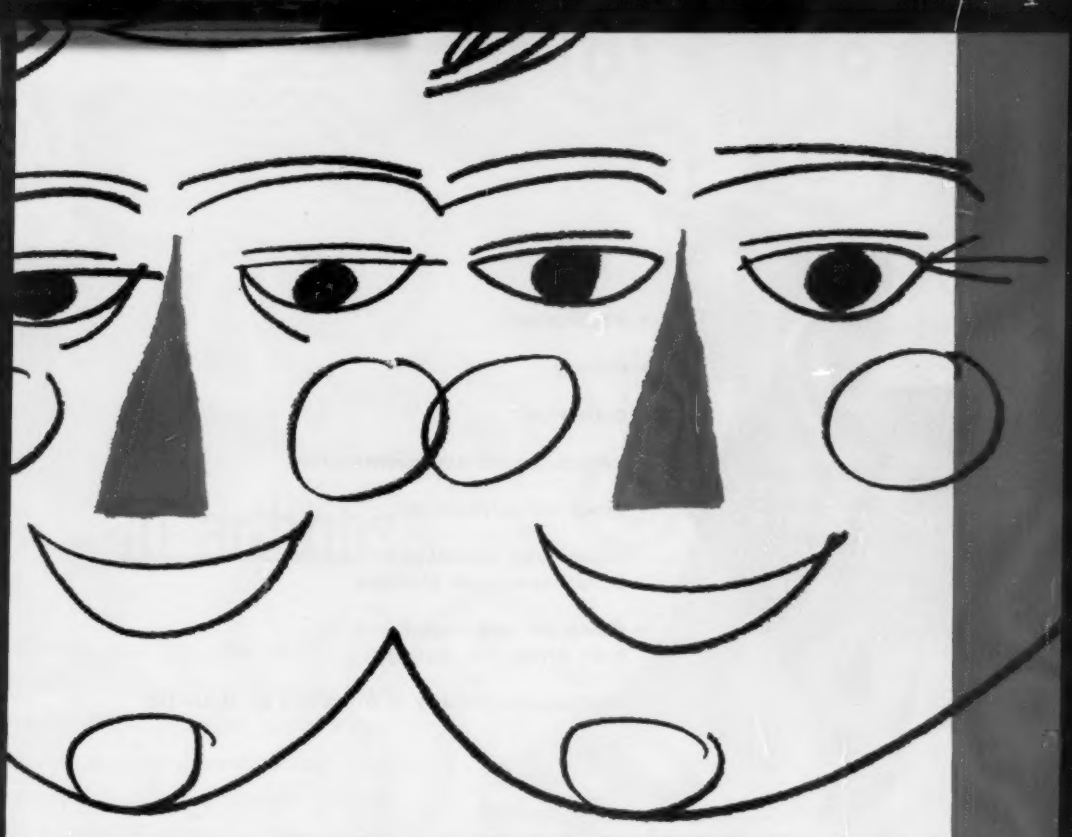

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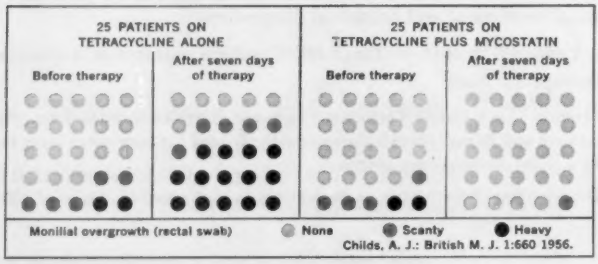

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Shingleton, et al; Surgery, 42: 12, 1957

Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956

Krane; Am. Pract. and Digest, 8: 1275, 1957

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1. Cecil, R.L., and Loeb, R.F.: A Textbook of Medicine. W.B. Saunders Co., Philadelphia, 1955, 9th ed., p. 870.

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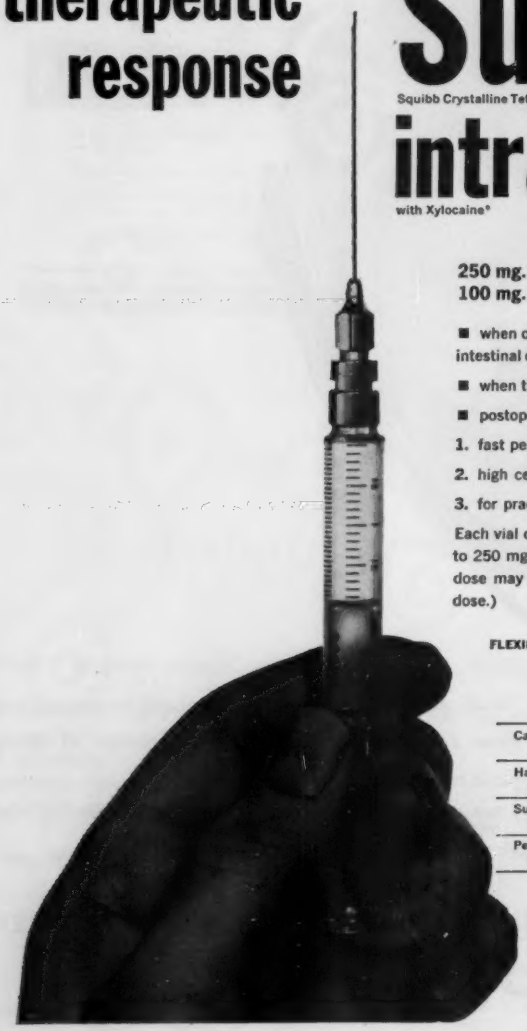

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- when oral therapy is contraindicated (vomiting, dysphagia, intestinal obstruction, gastrointestinal disorders)
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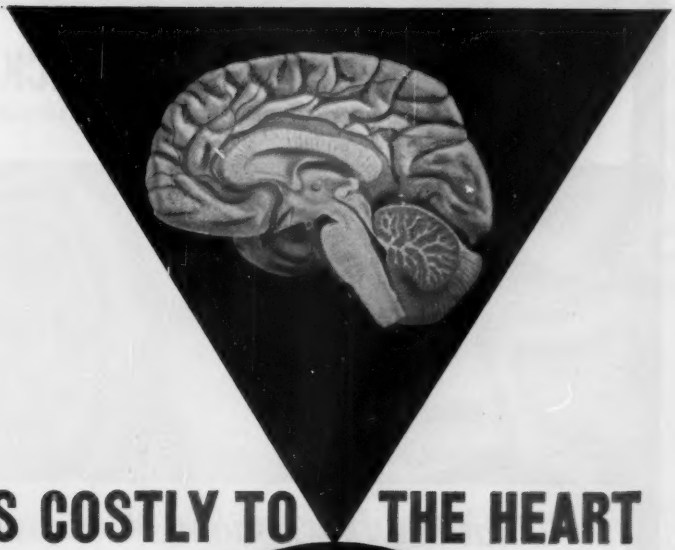

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Anxiety may precipitate tachycardia, various arrhythmias, coronary insufficiency, and increased cardiac decompensation.

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*Waldman, S. and Palmer, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.

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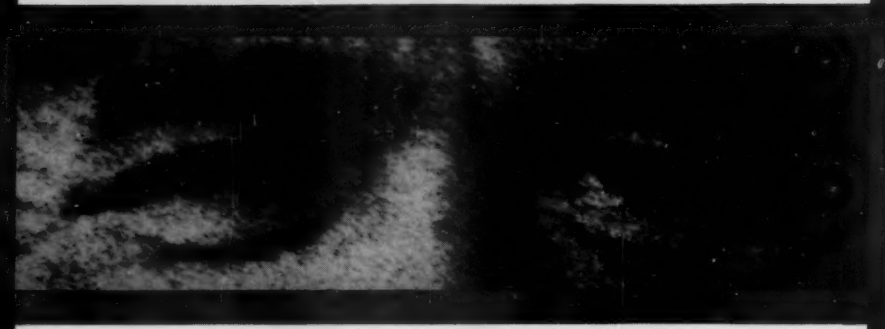

what are the 7 "dont's" of office psychotherapy?

(1) Don't argue—let patient "talk out" his troubles. (2) Don't counsel—help him solve his own problems. (3) Don't be hostile—allow patient to express hostility without reciprocating. (4) Don't be unsure—stress significance of normal or abnormal physical findings in relation to symptoms. (5) Don't be too reassuring—overoptimism may suggest you take the symptoms too lightly. (6) Don't approve or censure. (7) Don't be too credulous—patients' words may conceal hidden meanings.

Source—Hyman, M.: Some Aspects of Psychiatry in General Practice, GP *16*:83 (Oct.) 1957.

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for tranquil—not "tranquilized" patients

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*Bauer, H. G.; Seegers, W.; Krawzoff, M., and McGavack, T. H.: A Clinical Evaluation of Ectylurea (NOSTYN®), in press.

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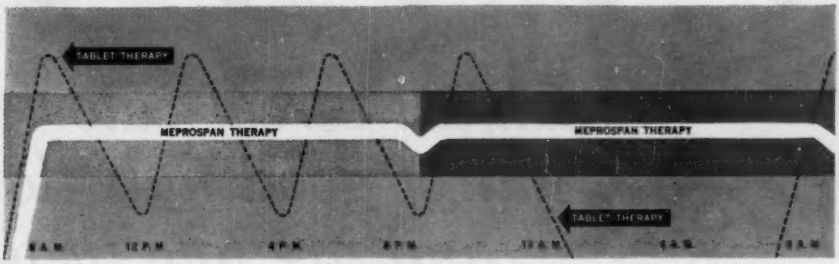

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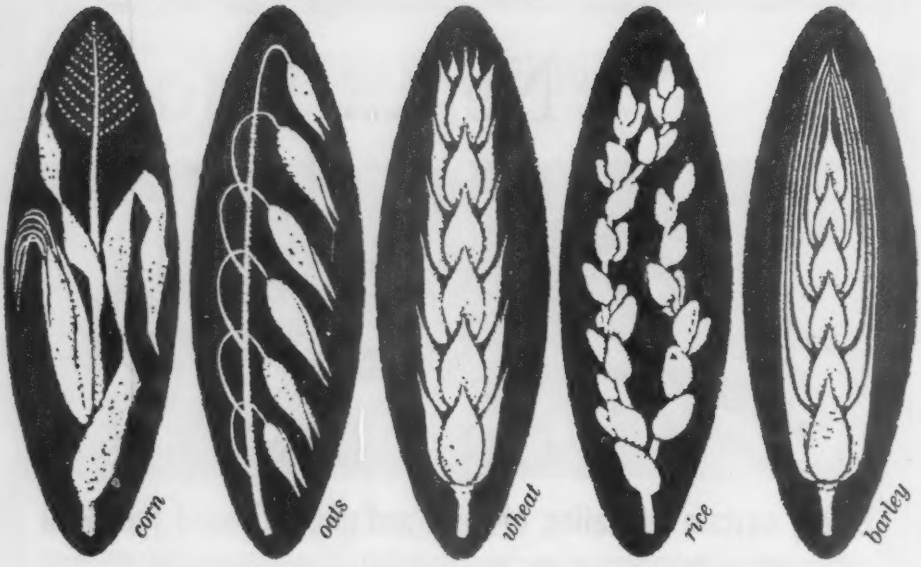

breakfast cereal calories are full of good nutrition and are low in fat

Medical and nutrition experts are concerned because the teen-age, elderly, and obese individuals are consuming too many empty calories. When a moderate reduction of dietary fat is indicated, breakfast cereal calories merit consideration because they provide *low-fat content* and are full of good nutrition as shown in the table below. Whole grain, enriched, and restored breakfast cereals, hot or ready to eat, considered as a group contribute protein, important B vitamins, and essential minerals in addition to the carbohydrates needed for quick energy.

nutritive value of breakfast cereals
(based on composite average)

	cereal, 1 oz. dry weight basis
CALORIES	104
PROTEIN	3.1 gm.
FAT	0.6 gm.
CARBOHYDRATE	22 gm.
IRON	1.4 mg.
THIAMINE	0.12 mg.
RIBOFLAVIN	0.04 mg.
NIACIN	1.3 mg.
CHOLESTEROL	0

Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.

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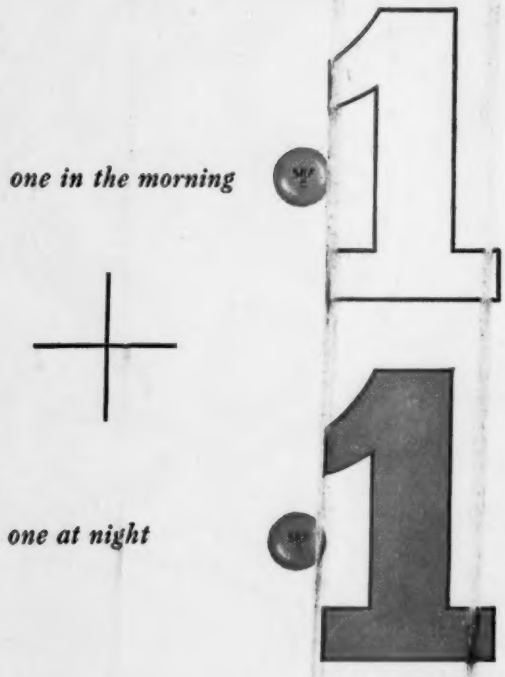

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1. Mullie, A.: The Inhibition of Basal Gastric Secretion and of the Gastric Secretory Response to Histamine by 2,2-Diphenyl-4-diisopropylamino-butyramide Methyliodide ['Darbid'] in Man, Arch. internat. pharmacodyn. *106*:447 (June) 1956.

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